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(54) Title: <b>STABILIZED UREASE INHIBITOR</b>			
(57) Abstract <p>In order to provide a stabilized urease inhibitor composition or preparation, is provided a pharmaceutical composition with an extended shelf-life which comprises a urease inhibitor and an oleaginous base, a gastrointestinal mucosa-adherent pharmaceutical composition comprising a viscogenic agent in addition to the above components, and preparations.</p>			

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DESCRIPTION

## Stabilized Urease Inhibitor

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TECHNICAL FIELD

The present invention relates to a stabilized pharmaceutical composition comprising a urease inhibitor and a preparation containing the pharmaceutical composition. The present invention further relates to a gastrointestinal mucosa-adherent pharmaceutical composition comprising an urease inhibitor. The pharmaceutical composition and dosage form of the present invention find application each as an anti-Helicobacter pylori preparation and/or as an antiulcerative preparation.

BACKGROUND ART

Since 1983 when Helicobacter pylori (hereinafter sometimes abbreviated as H. Pylori or HP) was first isolated [Lancet, 1, 1273 (1983)], its relation to gastritis and gastrointestinal ulcer has gathered attention. This is because whereas HP is not usually found in the gastric mucus and on the gastric epithelium of healthy humans [APMIS, 96, 84 (1983)], it is detected at a high rate among patients with chronic gastritis or gastric ulcer. [Am. J. Gastroenterol., 32, 2283 (1987)].

The cure rate of gastroduodenal ulcers rose phenomenally with the development of  $H_2$  blockers and proton pump inhibitors (briefly, PPI). However there still are refractory cases not even responding to judicious treatments with those drugs, thus posing a serious problem. According to a report reviewing such refractory gastric ulcer cases [Japanese Journal of Gastroenterology, 89, 571 (1992)], depressions were found in the amount of gastric mucus, apparently owing to the ammonia produced by HP. It

has also been reported that a sustained HP infection retards healing of the ulcer or is involved in relapses of the ulcer [Lancet, 335, 1233 (1990); N. Engl. J. Med., 328, 308 (1993)]. Thus, the well-documented findings, inclusive of 5 the above, suggest that clearance of HP contributes to an early cure or prevention of relapse of ulcers.

It is reported that microorganisms of the genus Helicobacter, particularly Helicobacter pylori, have high urease activity and that they are able to survive, even in 10 the stomach, by synthesizing ammonia from urea and thereby neutralizing the strongly acidic environment.

In the treatment of various diseases caused by HP, chemotherapy comprising a two-drug combination therapy using a bismuth drug and an antibiotic or a three-drug 15 combination therapy using a bismuth drug, metronidazole (USP 2,944,061) and either tetracycline (e.g. USP 2,712,517) or amoxicillin (USP 3,192,198) is practiced today. Metronidazole, mentioned above, is an imidazole derivative having anti-HP activity and has been used in 20 combination with antibiotics. The bismuth drug, antibiotic, metronidazole, etc. are generally administered by the oral route.

However, in order to insure a sustained and effective local concentration for inhibiting the growth of HP in their 25 habitat, said bismuth drugs, antibiotics, metronidazole, etc. must be administered in massive doses, daily. However this therapy entails many problems, for example side effects such as vomiting and diarrhea.

Meanwhile, many phosphoric amide derivatives having 30 urease inhibitory activity are known (USP 3,317,637, USP 4,517,003, USP 4,528,020, EP 210703, USP 4,182,881, USP 4,221,730, Japanese Patent Unexamined Publication No. 99490/1983, Japanese Patent Publication No. 7379/1967, USP 4,629,491, J. Pharm. Sci., 189, 57 (1968), etc.). However, 35 whether those phosphoric amide derivatives ever show antimicrobial activity, particularly anti-HP activity, in

vivo, is not known.

Under the circumstances, various drugs having anti-HP activity are currently administered to patients with gastroduodenal ulcers. Some proton pump inhibitors (PPIs) having anti-HP activity have also been developed but their anti-HP effects are not high enough and monotherapies using them have not been fully rewarding. On the other hand, combination therapies using an antiulcerative agent, such as an H<sub>2</sub> blocker, and a PPI in combination with an antimicrobial preparation have also been attempted with a fair success [e.g. Medical Journal of Australia, 151, 431 (1988), George L.L. et. al.; Medical Journal of Australia, 153, 145 (1990), Peterson W.L. et al.; New England Journal of Medicine, 324, 1043 (1991); and New England Journal of Medicine, 328, 308 (1993)].

Heretofore, as anti-HP agents, amoxicillin (hereinafter sometimes abbreviated as AMOX), metronidazole (briefly, MZ), bismuth acetate, and tetracycline have been used either independently or in combination but because they must be administered in massive doses (e.g. AMOX 750 mg or MZ 500mg, to be administered 3 times daily), those therapies entail side effects such as diarrhea, vomiting, and nausea with a fairly high frequency. There also is an apprehension about emergence of resistant bacteria.

On the other hand, combination therapies using a plurality of drugs having dissimilar mechanisms of action, such as administration of a pharmaceutical composition containing an anti-HP antibiotic substance (such as AMOX) and pantoprazole (WO 92/03135), or a combination therapy using amoxicillin and omeprazole [Scandinavian Journal of Gastroenterology, 24, 49 (1989)] are known, but their antiulcerative effects are not satisfactory enough and they involve side effects such as those mentioned above.

Meanwhile, a gastrointestinal mucosa-adherent matrix has been developed for ensuring a prolonged residence of the active ingredient and the consequent

improvement in availability of the ingredient. As the preferred active ingredient of such a preparation, an antiulcerative agent or a therapeutic drug for gastritis has been mentioned (Japanese Patent Unexamined Publication 5 No.132416/1993), and actually the preparation has been applied to a combination therapy using an antiulcerative agent and an antimicrobial agent (Japanese Patent Unexamined Publication No. 126189/1995). However, preparations including a urease inhibitor are not known.

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#### DISCLOSURE OF INVENTION

In view of the above state of the art, the inventors of the present invention did many investigations with the objective of developing a pharmaceutical composition 15 ensuring the stability and increased anti-HP efficacy of a urease inhibitor. As a result, they have discovered that a urease inhibitor, which is inherently acid-labile, can be stabilized in a composition, (particularly a matrix) comprising an oleaginous base, particularly a polyglycerol 20 fatty acid ester and/or a lipid. The inventors have further discovered that the efficacy of the urease inhibitor can be augmented either by incorporating a viscogenic agent capable of being viscous with water (hereinafter sometimes referred to as a viscogenic agent), in the matrix, or 25 coating the matrix with a coating composition containing the viscogenic agent. The present invention has been developed on the basis of the above findings.

The present invention, therefore, is directed to:

- (1) A pharmaceutical composition comprising a urease inhibitor and an oleaginous base,
- 30 (2) A pharmaceutical composition according to (1), which is a matrix,
- (3) A pharmaceutical composition according to (1), which is a gastrointestinal mucosa-adherent composition,
- 35 (4) A pharmaceutical composition according to (1), which is a gastrointestinal mucosa-adherent matrix.

(5) A pharmaceutical composition according to (1), wherein the oleaginous base is a polyglycerol fatty acid ester and/or a lipid.

5 (6) A pharmaceutical composition according to (5), wherein the polyglycerol fatty acid ester is an ester of a polyglycerol having a degree of polymerization ranging from about 2 to about 20 with a fatty acid containing about 8 to about 40 carbon atoms,

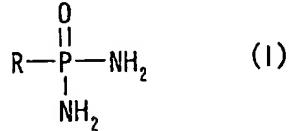
10 (7) A pharmaceutical composition according to (5), wherein the HLB number of the polyglycerol fatty acid ester is about 1 to about 9,

15 (8) A pharmaceutical composition according to (5), wherein the amount of the polyglycerol fatty acid ester and/or the lipid used is about 20 to about 95 weight% to the total weight of the composition,

20 (9) A pharmaceutical composition according to (1), wherein the amount of the urease inhibitor used is about 10 to about 50 weight% to the total weight of the composition,

(10) A pharmaceutical composition according to (1), wherein the urease inhibitor is a phosphoric amide derivative or a salt thereof,

25 (11) A pharmaceutical composition according to (10), wherein the phosphoric amide derivative is a compound of the formula (I):

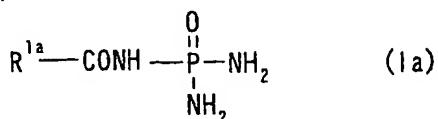


wherein R represents an amino group which may be substituted, or a salt thereof.

30 (12) A pharmaceutical composition according to (11), wherein R is a group represented by the formula:  
-NHCOR<sup>1</sup>

wherein R<sup>1</sup> represents hydrogen, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted,

(13) A pharmaceutical composition according to (10), wherein the phosphoric amide derivative is a compound of the formula (Ia):



5 wherein  $\text{R}^{1a}$  represents a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, or a salt thereof.

10 (14) A pharmaceutical composition according to (13), wherein  $\text{R}^{1a}$  represents an aromatic hydrocarbon group or an aromatic heterocyclic group, each of which may be substituted,

15 (15) A pharmaceutical composition according to (13), wherein  $\text{R}^{1a}$  represents a 5-membered aromatic heterocyclic group which may be substituted,

20 (16) A pharmaceutical composition according to (13), wherein  $\text{R}^{1a}$  represents a thienyl group or a furyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of a  $\text{C}_{1-3}$  alkyl group which may be substituted by 1 to 3 halogens, a  $\text{C}_{1-3}$  alkoxy group, halogen, nitro, cyano, a ( $\text{C}_{1-6}$  alkyl)carbonyl and ( $\text{C}_{1-6}$  alkyl)sulphonyl.

25 (17) A pharmaceutical composition according to (13), wherein  $\text{R}^{1a}$  represents a thienyl group or a furyl group, each of which is substituted by one or two  $\text{C}_{1-3}$  alkyl groups,

30 (18) A pharmaceutical composition according to (1), wherein the urease inhibitor is N-(diaminophosphinyl)-5-methyl-2-thiophenecarboxamide or a salt thereof,

(19) A pharmaceutical composition according to (1), wherein the urease inhibitor is N-(diaminophosphinyl)-2-methyl-3-furancarboxamide or a salt thereof,

35 (20) A pharmaceutical composition according to (1), wherein the urease inhibitor is N-(diaminophosphinyl)-5-methyl-3-furancarboxamide or a salt thereof,

(21) A pharmaceutical composition according to (1),

wherein the urease inhibitor is N-(diaminophosphinyl)-3,5-dimethyl-2-furancarboxamide or a salt thereof,

(22) A pharmaceutical composition according to (1), wherein the urease inhibitor is N-(diaminophosphinyl)-3,5-dimethyl-2-thiophenecarboxamide or a salt thereof,

(23) A pharmaceutical composition according to (4), wherein the matrix comprises a viscoelastic agent, capable of being viscous with water,

(24) A pharmaceutical composition according to (4), which is a matrix coated by a coating material containing a viscoelastic agent,

(25) A pharmaceutical composition according to (23), wherein the amount of the viscoelastic agent used is about 0.5 to about 30 weight% to the total weight of the composition,

(26) A pharmaceutical composition according to (23) or (24), wherein the viscoelastic agent is an acrylic polymer or a salt thereof,

(27) A pharmaceutical composition according to (9), wherein the urease inhibitor is an anti-Helicobacter pylori substance,

(28) A pharmaceutical composition according to (27), which is a preparation for the prophylaxis, treatment, or prevention of relapse of a Helicobacter pylori related gastrointestinal disease,

(29) A pharmaceutical composition according to (23), which comprises (i) a urease inhibitor, (ii) a polyglycerol fatty acid ester and/or a lipid, and (iii) an acrylic polymer, or a salt thereof,

(30) A pharmaceutical composition according to (29), wherein (i) the urease inhibitor is a compound of the formula (I), wherein R represents an amino group which may be substituted, or a salt thereof, (ii) the polyglycerol fatty acid ester and/or a lipid is behenic acid hexa(tetra)glyceride and/or tetraglycerol polyricinolate, and (iii) the molecular weight of the acrylic polymer is

about  $20 \times 10^4$  to about  $600 \times 10^4$ .

(31) A pharmaceutical composition according to (29), wherein (i) the urease inhibitor is a compound of the formula (Ia), wherein R<sup>1a</sup> represents a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, or a salt thereof, (ii) the polyglycerol fatty acid ester and/or a lipid is behenic acid hexa(tetra)glyceride and/or tetraglycerol polyricinolate, and (iii) the molecular weight of the acrylic polymer is about  $20 \times 10^4$  to about  $600 \times 10^4$ .

(32) A pharmaceutical composition according to (30), wherein R<sup>1a</sup> represents a thieryl group or a furyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-3</sub> alkyl group which may be substituted by 1 to 3 halogens, a C<sub>1-3</sub> alkoxy group, halogen, nitro, cyano, a (C<sub>1-6</sub> alkyl)carbonyl and (C<sub>1-6</sub> alkyl)sulphonyl.

(33) A pharmaceutical composition according to (30), wherein R<sup>1a</sup> represents a thieryl group or a furyl group, each of which is substituted by one or two C<sub>1-3</sub> alkyl groups.

(34) A pharmaceutical composition according to (1), which is used in combination with an antibiotic and/or an antacid and/or an acid secretion inhibitor.

(35) An anti-Helicobacter pylori composition which comprises the pharmaceutical composition according to (1),

(36) A pharmaceutical composition for the prophylaxis, treatment, and prevention of relapse of a Helicobacter pylori related gastrointestinal disease, comprising the pharmaceutical composition according to (1).

The present invention is further directed to a method of producing the composition and preparation and to the use of the composition and preparation.

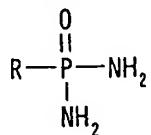
The present invention provides solid pharmaceutical compositions and preparations containing the composition, preferably as fine granules.

5 In the context of the present invention, the gastrointestinal mucosa-adherent matrix which is solid at room temperature includes the form in which each matrix particle comprising a polyglycerol fatty acid ester and/or a lipid and a active ingredient may be coated with a coating composition containing the viscoelastic agent.

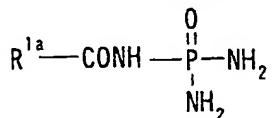
The invention further provides a technology for stabilizing acid-labile urease inhibitors.

10 The urease inhibitor for use in the present invention includes but is not limited to flurofamide (Micro. Ecol. Health Dis. 4 (suppl.) S145, 1991), the phosphoric amide derivatives described in the literature (USP 3,317,637 etc.), hydroxamic acid derivatives (the 15th Medicinal Chemistry Symposium, Synopsis of Lectures at the 4th Annual 15 Meeting of Medicinal Chemistry Group, page 167, P-41), etc., and plant extracts such as cassia extract (Synopsis of Lectures at the 117th Congress of the Pharmaceutical Society of Japan, 27 [H1] 9-5, p.81, 1997). Among them, phosphoric amide derivatives are particularly suitable for 20 the purposes of the invention.

The phosphoric amide derivative can include compounds of the formula (I):



25 wherein R represents an amino group which may be substituted, inclusive of their pharmaceutical acceptable salts, and preferably compounds of the formula (Ia):



30 wherein R<sup>Ia</sup> represents a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, inclusive of their pharmaceutical acceptable salts.

With respect to the above formulas, the substituents in the "amino group which may be substituted" represented by R are exemplified by (1) acyl groups, (2) carboxyl groups which may be esterified, and (3) hydrocarbon groups which may be substituted. The amino group may be substituted by 5 1 or 2, preferably 1 of these substituents, whether identical or not. The substituents are preferably an acyl group or a carboxyl group which may be esterified, more preferably an acyl group.

(1) The acyl group as a substituent in the "amino group which may be substituted" represented by R, is exemplified by acyl groups derived from carboxylic acids, thiocarboxylic acids, sulfonic acids, sulfinic acids, carbamic acids, thiocarbamic acids etc., specifically 15 those represented by the respective formulas: -COR<sup>1</sup>, -CSR<sup>2</sup>, -SO<sub>2</sub>R<sup>3</sup>, -SOR<sup>4</sup>, -CONHR<sup>5</sup> or -CSNHR<sup>6</sup>, wherein R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> independently represent a hydrogen atom, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, etc. 20 Preferable acyl groups include those derived from carboxylic acids (-COR<sup>1</sup>) and those derived from sulfonic acids (-SO<sub>2</sub>R<sup>3</sup>), and those derived from carboxylic acids are more preferable.

25 The "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup>, is exemplified by saturated or unsaturated aliphatic chain hydrocarbon groups, saturated or unsaturated alicyclic hydrocarbon groups and aryl groups.

30 Such saturated aliphatic hydrocarbon groups include straight-chain or branched saturated aliphatic hydrocarbon groups having 1 to 10 carbon atoms (e.g., C<sub>1-10</sub> alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, 35 tert-pentyl, hexyl, isohexyl, heptyl and octyl), and straight-chain or branched saturated aliphatic hydrocarbon

groups having 1 to 6 carbon atoms are preferable.

Such unsaturated aliphatic hydrocarbon groups include straight-chain or branched unsaturated aliphatic hydrocarbon groups having 2 to 10 carbon atoms (e.g., C<sub>2-10</sub> alkenyl groups such as ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methyl-1-propenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 3-methyl-2-butenyl, 1-hexenyl, 3-hexenyl, 2,4-hexadienyl, 5-hexenyl, 1-heptenyl and 1-octenyl; C<sub>2-10</sub> alkynyl groups such as ethynyl, 1-propynyl, 2-propynyl, 1-butynyl, 2-butynyl, 3-butynyl, 1-pentynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 1-hexynyl, 3-hexynyl, 2,4-hexadiynyl, 5-hexynyl, 1-heptynyl and 1-octynyl), and straight-chain or branched unsaturated aliphatic hydrocarbon groups having 2 to 6 carbon atoms are preferable.

Such saturated alicyclic hydrocarbon groups include saturated alicyclic hydrocarbon groups having 3 to 12 carbon atoms (e.g., monocyclic or bicyclic C<sub>3-12</sub> cycloalkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, bicyclo[3.2.2]nonyl, bicyclo[3.3.1]nonyl, bicyclo[4.2.1]nonyl and bicyclo[4.3.1]decyl), and saturated alicyclic hydrocarbon groups having 3 to 6 carbon atoms are preferable.

Such unsaturated alicyclic hydrocarbon groups include unsaturated alicyclic hydrocarbon groups having 5 to 12 carbon atoms (e.g., C<sub>5-12</sub> cycloalkenyl groups such as 1-cyclopentenyl, 2-cyclopentenyl, 3-cyclopentenyl, 1-cyclohexenyl, 2-cyclohexenyl, 3-cyclohexenyl, 1-cycloheptenyl, 2-cycloheptenyl, 3-cycloheptenyl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2-cyclohexen-1-yl and 3-cyclohexen-1-yl; C<sub>5-12</sub> cycloalkadienyl groups such as 2,4-cyclopentadien-1-yl, 2,4-cyclohexadien-1-yl and 2,5-cyclohexadien-1-yl and 2,4-cycloheptadienyl).

The hydrocarbon group in the "hydrocarbon group which

may be substituted" may be a saturated aliphatic hydrocarbon group having 1 to 8 carbon atoms substituted by the above saturated or unsaturated alicyclic hydrocarbon group (e.g., C<sub>3-7</sub> cycloalkyl-C<sub>1-8</sub> alkyl groups and C<sub>5-7</sub> cycloalkenyl-C<sub>1-8</sub> alkyl groups, such as cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl, 2-cyclopentenylmethyl, 3-cyclopentenylmethyl, cyclohexylmethyl, 2-cyclohexenylmethyl, 3-cyclohexenylmethyl, cyclohexylethyl, cyclohexylpropyl, cycloheptylmethyl and cycloheptylethyl), or the like.

Such aryl groups include monocyclic or fused polycyclic aromatic hydrocarbon ring groups having 6 to 14 carbon atoms. Such aromatic hydrocarbon ring groups include phenyl, 1- or 2-naphthyl, 1-, 2- or 9-anthryl, 1-, 2-, 3-, 4- or 9-phenanthryl, 1-, 2-, 4-, 5- or 6-azulenyl and acenaphthylene, and C<sub>6-10</sub> aryl groups such as phenyl, 1-naphthyl and 2-naphthyl are preferable.

The "hydrocarbon group which may be substituted" may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include (1) lower alkyl groups which may be substituted, (2) lower alkoxy groups which may be substituted, (3) aryl groups which may be substituted, (4) lower cycloalkyl or lower cycloalkenyl groups which may be substituted, (5) heterocyclic groups which may be substituted, (6) carboxyl groups which may be esterified, (7) carbamoyl groups which may be substituted, (8) amino groups which may be substituted, (9) hydroxyl groups which may be substituted, (10) thiol (mercapto) groups which may be substituted, (11) acyl groups, (12) halogens (e.g., fluorine, chlorine, bromine), (13) nitro, and (14) cyano.

The lower alkyl group in the lower alkyl group (1) which may be substituted, is exemplified by C<sub>1-6</sub> alkyl groups such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl

and isohexyl.

The lower alkoxy group in the lower alkoxy group (2) which may be substituted, is exemplified by C<sub>1-6</sub> alkoxy groups such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, 5 isobutoxy, sec-butoxy, tert-butoxy, pentoxy, isopentoxy, neopentoxy, hexyloxy and isohexyloxy.

Said lower alkyl group (1) and lower alkoxy group (2) may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include halogens 10 (e.g., fluorine, chlorine, bromine) and lower (C<sub>1-3</sub>) alkoxy groups (e.g., methoxy, ethoxy, propoxy).

The aryl group in the aryl group (3) which may be substituted, is exemplified by C<sub>6-14</sub> aryl groups such as phenyl, naphthyl, anthryl, phenanthryl and acenaphthyl, 15 phenyl, 1-naphthyl and 2-naphthyl are preferable among others.

The cycloalkyl group in the lower cycloalkyl group (4) which may be substituted, is exemplified by C<sub>3-7</sub> cycloalkyl groups such as cyclopropyl, cyclobutyl, 20 cyclopentyl, cyclohexyl and cycloheptyl.

The cycloalkenyl group in the lower cycloalkenyl group (4) which may be substituted, is exemplified by C<sub>3-6</sub> cycloalkenyl groups such as cyclopropenyl, cyclobutenyl, cyclopentenyl and cyclohexenyl.

Said aryl group (3), said lower cycloalkyl group (4) or said lower cycloalkenyl group (4) may have 1 to 5, 25 preferably 1 to 3, optionally chosen substituents at any possible positions, and these substituents include alkoxy groups (e.g., C<sub>1-3</sub> alkoxy groups such as methoxy, ethoxy and propoxy), halogen atoms (e.g., fluorine, chlorine, bromine, iodine), alkyl groups (e.g., C<sub>1-3</sub> alkyl groups such as methyl, ethyl and propyl), amino, nitro and cyano.

The heterocyclic group in the heterocyclic group (5) 35 which may be substituted, is exemplified by aromatic heterocyclic groups and saturated or unsaturated non-

aromatic heterocyclic groups (aliphatic heterocyclic groups) having at least 1 hetero atom selected from oxygen, sulfur and nitrogen as a ring-constituting atom (ring atom), and aromatic heterocyclic groups are preferable. Such aromatic heterocyclic groups include 5- to 7-membered aromatic heterocyclic groups containing 1 sulfur atom, nitrogen atom or oxygen atom, 5- or 6-membered aromatic heterocyclic groups containing 2 to 4 nitrogen atoms, and 5- or 6-membered aromatic heterocyclic groups containing 1 or 2 nitrogen atoms and 1 sulfur atom or oxygen atom. These aromatic heterocyclic groups may be fused with a 6-membered ring containing 2 or fewer nitrogen atoms, a benzene ring, or a 5-membered ring containing 1 sulfur atom. Such aromatic heterocyclic groups include aromatic monocyclic heterocyclic groups (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl) and aromatic fused heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl,  $\alpha$ -carbolinyl,  $\beta$ -carbolinyl,  $\gamma$ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl), and preferable are furyl, fused furyl,

thienyl, fused thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl, azolyl and fused azolyl groups thereof. The azolyl groups include 5-membered aromatic heterocyclic groups containing 1 to 4 nitrogen atoms (e.g., 5 pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl) and 5-membered aromatic heterocyclic groups containing 1 or 2 nitrogen atoms and 1 sulfur atom or oxygen atom (e.g., oxazolyl, isoxazolyl, thiazolyl, isothiazolyl), and the fused azolyl groups include groups formed by fusion of a 10 benzene ring with a 5-membered aromatic heterocyclic ring containing 1 or 2 nitrogen atoms (e.g., benzimidazolyl) and groups formed by fusion of a benzene ring with a 5-membered aromatic heterocyclic ring containing 1 nitrogen atom and 1 sulfur atom or oxygen atom (e.g., benzoxazolyl, 15 benzisoxazolyl, benzothiazolyl, benzisothiazolyl). Particular preferred are furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, benzo[b]thienyl, oxazolyl and isoxazolyl, 20 and furyl and thienyl are more preferred.

Such non-aromatic heterocyclic groups include 5- to 7-membered non-aromatic heterocyclic groups containing 1 sulfur atom, nitrogen atom or oxygen atom, and 3- to 7-membered non-aromatic heterocyclic groups containing 1 nitrogen atom and 3 or fewer hetero atoms (e.g., nitrogen, 25 oxygen and sulfur atoms), such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperidyl, pyrrolinyl, 30 and imidazolidinyl. These non-aromatic heterocyclic groups may be fused with a benzene ring, a 6-membered ring containing 2 or fewer nitrogen atoms, a 5-membered ring containing 1 sulfur atom, or the like. Such fused non-aromatic heterocyclic groups include chromanyl, 35 isochromanyl, indolinyl, isoindolinyl, thiochromanyl and isothiochromanyl.

The heterocyclic groups may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include alkoxy groups (e.g., C<sub>1-4</sub> alkoxy groups such as methoxy, ethoxy and propoxy) which may be substituted by 1 to 3 halogen atoms (e.g. fluorine, chlorine, bromine, iodine), halogen atoms (e.g., fluorine, chlorine, bromine, iodine), alkyl groups (e.g., C<sub>1-4</sub> alkyl groups such as methyl, ethyl and propyl) which may be substituted by 1 to 3 halogen atoms (e.g. fluorine, chlorine, bromine, iodine), aryl groups (e.g., C<sub>6-10</sub> aryl groups such as phenyl, 1-naphthyl and 2-naphthyl), and nitro.

The carboxyl group (6) which may be esterified include carboxyl groups, (lower (C<sub>1-6</sub>) alkoxy)carbonyl groups (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, sec-butoxycarbonyl, pentyloxycarbonyl, isopentyloxycarbonyl, neopentyloxycarbonyl, tert-pentyloxycarbonyl, hexyloxycarbonyl), (C<sub>6-10</sub> aryl)oxygen carbonyl groups (e.g., phenoxy carbonyl, 1-naphthoxycarbonyl) and (C<sub>7-10</sub> aralkyl)oxygen carbonyl group (e.g., (phenyl-C<sub>1-4</sub> alkyl)oxygen carbonyl groups such as benzyloxycarbonyl etc.), and the carboxyl group, methoxycarbonyl and ethoxycarbonyl are preferred.

The substituents in said carbamoyl group (7) which may be substituted, or in the amino group (8) which may be substituted, are exemplified by lower (C<sub>1-6</sub>) alkyl groups which may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, isohexyl), C<sub>3-6</sub> cycloalkyl groups which may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C<sub>6-10</sub> aryl groups which may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl), C<sub>7-12</sub> aralkyl groups which may be substituted (e.g., phenyl-C<sub>1-4</sub> alkyl groups such as benzyl and phenethyl,

and naphthyl-C<sub>1-2</sub> alkyl groups), and C<sub>6-10</sub> arylsulfonyl groups which may be substituted (e.g., benzenesulfonyl, 1-naphthalenesulfonyl, 2-naphthalenesulfonyl), and 1 or 2 of these substituents, whether identical or not, may be present. The substituents in such lower (C<sub>1-6</sub>) alkyl groups which may be substituted, C<sub>3-6</sub> cycloalkyl groups which may be substituted, C<sub>6-10</sub> aryl groups which may be substituted, C<sub>7-12</sub> aralkyl groups which may be substituted, and C<sub>6-10</sub> arylsulfonyl groups which may be substituted, include 5 halogens (e.g., fluorine, chlorine, bromine), alkoxy groups (e.g., C<sub>1-4</sub> alkoxy groups such as methoxy, ethoxy and propoxy) which may be substituted by 1 to 3 halogens, alkyl groups (e.g., C<sub>1-4</sub> alkyl groups such as methyl, ethyl and propyl) which may be substituted by 1 to 3 halogens, and 10 nitro, and 1 to 5 of these substituents may be present. Also, the amino group which may be substituted, may form a cyclic amino group resulting from binding of two substituents on the nitrogen atom with the nitrogen atom, and such cyclic 15 amino groups include 1-azetidinyl, 1-pyrrolidinyl, 20 piperidino, morpholino and 1-piperazinyl.

The substituents in said hydroxyl group (9) which may be substituted, and the thiol group (10) which may be substituted, are exemplified by hydrocarbon groups which may be substituted, and heterocyclic groups which may be substituted. The "hydrocarbon group which may be substituted" is exemplified by the same groups as those mentioned in the "hydrocarbon group which may be substituted," represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above, 25 and preferable are lower (C<sub>1-6</sub>) alkyl groups which may be substituted (e.g., methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, 30 isopentyl, hexyl, isohexyl), C<sub>3-6</sub> cycloalkyl groups which may be substituted (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl), C<sub>6-10</sub> aryl groups which may be substituted (e.g., phenyl, 1-naphthyl, 2-naphthyl), and 35

C<sub>7-12</sub> aralkyl groups which may be substituted (e.g., phenyl-C<sub>1-4</sub> alkyl groups such as benzyl and phenethyl, and naphthyl-C<sub>1-2</sub> alkyl groups). These lower (C<sub>1-6</sub>) alkyl groups, C<sub>3-6</sub> cycloalkyl groups, C<sub>6-10</sub> aryl groups and C<sub>7-12</sub> aralkyl groups may have 1 to 5 optionally chosen 5 substituents at any possible positions, and these substituents include halogens (e.g., fluorine, chlorine, bromine), alkoxy groups (e.g., C<sub>1-4</sub> alkoxy groups such as methoxy, ethoxy and propoxy) which may be substituted by 10 1 to 3 halogens, alkyl groups (e.g., C<sub>1-4</sub> alkyl groups such as methyl, ethyl and propyl) which may be substituted by 1 to 3 halogens, nitro, amino and cyano. The "heterocyclic 15 group which may be substituted" is exemplified by the same groups as those mentioned below in the "heterocyclic group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup>.

The acyl group (11) is exemplified by formyl groups, carbonyl groups substituted by a hydrocarbon group which may be substituted, sulfinyl groups substituted by a hydrocarbon group which may be substituted, and sulfonyl 20 groups substituted by a hydrocarbon group which may be substituted. The "hydrocarbon group which may be substituted" is exemplified by the same groups as those mentioned in the "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above, and preferable are lower (C<sub>1-6</sub>) alkyl groups which may be substituted, C<sub>3-6</sub> cycloalkyl groups which may be substituted, C<sub>6-10</sub> aryl groups (e.g., phenyl, naphthyl) which may be substituted, and C<sub>7-12</sub> aralkyl groups (e.g., phenyl-C<sub>1-4</sub> 25 alkyl groups, naphthyl-C<sub>1-2</sub> alkyl groups) which may be substituted. Preferable acyl groups include formyl groups, (C<sub>1-6</sub> alkyl)carbonyl groups, (C<sub>3-6</sub> cycloalkyl)carbonyl groups, (C<sub>6-10</sub> aryl)carbonyl groups, (C<sub>7-12</sub> aralkyl)carbonyl groups, (C<sub>1-6</sub> alkyl)sulfinyl groups (C<sub>3-6</sub> 30 cycloalkyl)sulfinyl groups, (C<sub>6-10</sub> aryl)sulfinyl groups, (C<sub>7-12</sub> aralkyl)sulfinyl groups, (C<sub>1-6</sub> alkyl)sulfonyl groups, (C<sub>3-6</sub> cycloalkyl)sulfonyl groups, (C<sub>6-10</sub> aryl)sulfonyl groups, (C<sub>7-12</sub> aralkyl)sulfonyl groups. 35

(C<sub>3-6</sub> cycloalkyl)sulfonyl groups, (C<sub>6-10</sub> aryl)sulfonyl groups and (C<sub>7-12</sub> aralkyl)sulfonyl groups. These acyl groups may have 1 to 5 optionally chosen substituents at any possible positions, and such substituents include 5 halogens, alkoxy group (e.g., C<sub>1-4</sub> alkoxy groups) and alkyl groups (e.g., C<sub>1-4</sub> alkyl groups).

The heterocyclic group in the "heterocyclic group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup>, is exemplified by aromatic heterocyclic groups and 10 saturated or unsaturated non-aromatic heterocyclic groups (aliphatic heterocyclic groups) having at least 1 hetero atom selected from atoms of oxygen, sulfur and nitrogen as a ring-constituting atom (ring atom), and aromatic heterocyclic groups are preferred.

Such aromatic heterocyclic groups include 5- to 15 7-membered aromatic heterocyclic groups containing 1 sulfur atom, nitrogen atom or oxygen atom, 5- or 6-membered aromatic heterocyclic groups containing 2 to 4 nitrogen atoms, and 5- or 6-membered aromatic heterocyclic groups 20 containing 1 or 2 nitrogen atoms and 1 sulfur atom or oxygen atom. These aromatic heterocyclic groups may be fused with a 6-membered ring containing 2 or fewer nitrogen atoms, a benzene ring, or a 5-membered ring containing 1 sulfur atom. Such aromatic heterocyclic groups include aromatic 25 monocyclic heterocyclic groups (e.g., furyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, imidazolyl, pyrazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, furazanyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 30 1,2,3-triazolyl, 1,2,4-triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl) and aromatic fused heterocyclic groups (e.g., benzofuranyl, isobenzofuranyl, benzo[b]thienyl, indolyl, isoindolyl, 1H-indazolyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, 1,2-benzisothiazolyl, 35 1H-benzotriazolyl, quinolyl, isoquinolyl, cinnolinyl,

quinazolinyl, quinoxalinyl, phthalazinyl, naphthyridinyl, purinyl, pteridinyl, carbazolyl,  $\alpha$ -carbolinyl,  $\beta$ -carbolinyl,  $\gamma$ -carbolinyl, acridinyl, phenoxazinyl, phenothiazinyl, phenazinyl, phenoxathiinyl, thianthrenyl, phenanthridinyl, phenanthrolinyl, indolizinyl, pyrrolo[1,2-b]pyridazinyl, pyrazolo[1,5-a]pyridyl, imidazo[1,2-a]pyridyl, imidazo[1,5-a]pyridyl, imidazo[1,2-b]pyridazinyl, imidazo[1,2-a]pyrimidinyl, 1,2,4-triazolo[4,3-a]pyridyl and 1,2,4-triazolo[4,3-b]pyridazinyl), and furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl, azolyl and fused ring groups thereof are preferred. Particularly furyl, thienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl, benzofuranyl, benzimidazolyl, benzoxazolyl, 1,2-benzisoxazolyl, benzothiazolyl, benzo[b]thienyl, oxazolyl and isoxazolyl are preferred, and furyl and thienyl are more preferred.

Such non-aromatic heterocyclic groups include 5- to 7-membered non-aromatic heterocyclic groups containing 1 sulfur atom, nitrogen atom or oxygen atom, and 3- to 7-membered non-aromatic heterocyclic groups containing 1 nitrogen atom and 3 or fewer hetero atoms (e.g., nitrogen, oxygen and sulfur atoms), such as oxiranyl, azetidinyl, oxetanyl, thietanyl, pyrrolidinyl, tetrahydrofuryl, thiolanyl, piperidyl, tetrahydropyranyl, morpholinyl, thiomorpholinyl, piperazinyl, homopiperidyl, pyrrolinyl and imidazolidinyl. These non-aromatic heterocyclic groups may be fused with a benzene ring, a 6-membered ring containing 2 or fewer nitrogen atoms, a 5-membered ring containing 1 sulfur atom, or the like. Such fused non-aromatic heterocyclic groups include chromanyl, isochromanyl, indolinyl, isoindolinyl, thiochromanyl and isothiochromanyl.

which may be substituted" represented by  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  or  $R^6$  above, may have 1 to 4, preferably 1 to 3, optionally chosen substituents at any possible positions. Such substituents include (i) lower alkyl groups which may be substituted, (ii) lower alkoxy groups which may be substituted, (iii) aryl groups which may be substituted, (iv) lower cycloalkyl or lower cycloalkenyl groups which may be substituted, (v) heterocyclic groups which may be substituted, (vi) carboxyl groups which may be esterified, (vii) carbamoyl groups which may be substituted, (viii) amino groups which may be substituted, (ix) hydroxyl groups which may be substituted, (x) thiol groups which may be substituted, (xi) acyl groups, (xii) halogens (e.g., fluorine, chlorine, bromine), (xiii) nitro, and (xiv) cyano.

The lower alkyl group (i) which may be substituted, the lower alkoxy group (ii) which may be substituted, the aryl group (iii) which may be substituted, the lower cycloalkyl group or lower cycloalkenyl group (iv) which may be substituted, the heterocyclic group (v) which may be substituted, the carboxyl group (vi) which may be esterified, the carbamoyl group (vii) which may be substituted, the amino group (viii) which may be substituted, the hydroxyl group (ix) which may be substituted, the thiol group (x) which may be substituted, and the acyl group (xi), are exemplified by the same substituents as those mentioned in the substituents in the "heterocyclic group which may be substituted" represented by  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  or  $R^6$  above.

Particularly preferable for  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  and  $R^6$  are alkyl groups which may be substituted (preferably  $C_{1-4}$  alkyl groups), alkenyl groups which may be substituted (preferably  $C_{2-4}$  alkenyl groups), aryl groups which may be substituted (preferably  $C_{6-10}$  aryl groups such as phenyl, 1-naphthyl and 2-naphthyl), and aromatic heterocyclic

groups which may be substituted (preferably furyl, benzofuranyl, thienyl, benzothienyl, indolyl, isoindolyl, pyrazinyl, pyridyl, pyrimidinyl, azolyl, or fused azolyl).

These alkyl groups, alkenyl groups and aryl groups  
5 may have 1 to 3 (preferably 1 to 2) optionally chosen  
substituents at any possible positions. Preferable  
substituents include (1) lower ( $C_{1-3}$ ) alkyl groups (e.g.,  
methyl, ethyl, propyl, isopropyl) which may be substituted  
by 1 to 3 halogens (e.g., fluorine, chlorine, bromine,  
10 iodine), (2) lower ( $C_{1-3}$ ) alkoxy groups (e.g., methoxy,  
ethoxy, propoxy, isopropoxy), (3)  $C_{6-10}$  aryl groups (e.g.,  
phenyl) which may be substituted by 1 to 3, preferably 1  
to 2, substituents selected from halogens (e.g. fluorine,  
chlorine, bromine, iodine), amino, nitro and cyano, (4)  $C_{6-10}$   
15 aryloxy groups (e.g., phenoxy) which may be substituted by  
1 to 3, preferably 1 to 2, substituents selected from lower  
( $C_{1-3}$ ) alkoxy groups (e.g., methoxy, ethoxy, propoxy,  
isopropoxy), halogens (e.g., fluorine, chlorine, bromine,  
iodine), nitro, cyano and amino, (5) heterocyclic groups  
20 (e.g., thienyl, benzimidazolyl, benzoxazolyl) which may be  
substituted by 1 to 3, preferably 1 to 2, halogens (e.g.,  
fluorine, chlorine, bromine, iodine), (6) amino groups  
which may be substituted by a p-toluenesulfonyl group etc.,  
(7) hydroxyl groups, (8) thiol groups which may be  
25 substituted by a  $C_{6-10}$  aryl groups (e.g. phenyl) which may  
have 1 to 3 (preferably 1 to 2) substituents selected from  
halogens and lower ( $C_{1-3}$ ) alkoxy groups, or thiol groups  
which may be substituted by a heterocyclic group (e.g.,  
benzoxazolyl, benzothiazolyl) which may have 1 to 3  
30 (preferably 1 to 2) substituents selected from halogens and  
lower ( $C_{1-3}$ ) alkoxy groups, (9) halogens (e.g., fluorine,  
chlorine, bromine), (10) nitro, and (11) cyano.

These aromatic heterocyclic groups may have 1 to 3  
(preferably 1 to 2) optionally chosen substituents at any  
35 possible positions. Preferable substituents include (1)  
lower ( $C_{1-3}$ ) alkyl groups which may be substituted by 1 to

3 halogens (e.g., methyl, ethyl, propyl, isopropyl, fluoromethyl, chloromethyl), (2) C<sub>6-10</sub> aryl groups (e.g., phenyl), (3) lower (C<sub>1-3</sub>) alkoxy groups which may be substituted by 1 to 3 halogens (e.g., methoxy, ethoxy, 5 propoxy, iso-propoxy, fluoromethoxy, chloromethoxy), (4) halogens (e.g., fluorine, chlorine, bromine), (5) nitro, (6) cyano, (7) (lower (C<sub>1-6</sub>)alkyl)carbonyl groups and (8) (C<sub>1-6</sub> alkyl)sulfonyl groups.

10 (2) The "carboxyl group which may be esterified" as a substituent in the "amino group which may be substituted" represented by R, is exemplified by groups represented by the formula: -COOR<sup>7</sup>, wherein R<sup>7</sup> represents a hydrogen atom, a hydrocarbon group which may be substituted or a 15 heterocyclic group which may be substituted.

Said hydrocarbon group is exemplified by the same groups as those mentioned in the "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above. Said hydrocarbon group may have 1 to 3 optionally 20 chosen substituents at any possible positions. Such substituents include lower alkyl groups which may be substituted, lower alkoxy groups which may be substituted, aryl groups which may be substituted, lower cycloalkyl groups or lower cycloalkenyl groups which may be 25 substituted, heterocyclic groups which may be substituted, carboxyl groups which may be esterified, carbamoyl groups which may be substituted, amino groups which may be substituted, hydroxyl groups which may be substituted, thiol groups which may be substituted, acyl groups, 30 halogens (e.g., fluorine, chlorine, bromine), nitro, and cyano.

Such lower alkyl groups which may be substituted, lower alkoxy groups which may be substituted, aryl groups which may be substituted, lower cycloalkyl groups or lower 35 cycloalkenyl groups which may be substituted, heterocyclic groups which may be substituted, carboxyl groups which may

be esterified, carbamoyl groups which may be substituted, amino groups which may be substituted, hydroxyl groups which may be substituted, thiol groups which may be substituted, and acyl groups, are exemplified by the same substituents as those mentioned in the substituent in the 5 "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above.

Said heterocyclic group is exemplified by the same 10 groups as those mentioned in the heterocyclic group in the "heterocyclic group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above. Said heterocyclic group may have 1 to 3 optionally chosen substituents at any 15 possible positions. Such substituents include lower alkyl groups which may be substituted, lower alkoxy groups which may be substituted, aryl groups which may be substituted, lower cycloalkyl groups or lower cycloalkenyl groups which may be substituted, heterocyclic groups which may be substituted, carboxyl groups which may be esterified, 20 carbamoyl groups which may be substituted, amino groups which may be substituted, hydroxyl groups which may be substituted, thiol groups which may be substituted, acyl groups, halogens (e.g., fluorine, chlorine, bromine), nitro, and cyano.

Such lower alkyl groups which may be substituted, 25 lower alkoxy groups which may be substituted, aryl groups which may be substituted, lower cycloalkyl groups or lower cycloalkenyl groups which may be substituted, heterocyclic groups which may be substituted, carboxyl groups which may be substituted, 30 be esterified, carbamoyl groups which may be substituted, amino groups which may be substituted, hydroxyl groups which may be substituted, thiol groups which may be substituted, and acyl groups, are exemplified by the same substituents as those mentioned in the substituent in the 35 "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above.

Preferably groups for R<sup>7</sup> include lower (C<sub>1-6</sub>) alkyl groups which may be substituted, lower (C<sub>3-6</sub>) cycloalkyl groups, C<sub>6-10</sub> aryl groups, and C<sub>7-12</sub> aralkyl groups, and lower (C<sub>1-3</sub>) alkyl groups are more preferable.

5 Such lower (C<sub>1-6</sub>) alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl and isohexyl.

Such lower (C<sub>3-6</sub>) cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

10 Such C<sub>6-10</sub> aryl groups include phenyl, 1-naphthyl and 2-naphthyl.

Such C<sub>7-12</sub> aralkyl groups include phenyl-C<sub>1-4</sub> alkyl groups such as benzyl and phenethyl, and naphthyl-C<sub>1-2</sub> alkyl groups.

15 These lower (C<sub>1-6</sub>) alkyl groups, lower (C<sub>3-6</sub>) cycloalkyl groups, C<sub>6-10</sub> aryl groups and C<sub>7-12</sub> aralkyl groups may have 1 to 3 optionally chosen substituents at any possible positions, and these substituents include halogens (e.g., fluorine, chlorine, bromine).

20 (3) The "hydrocarbon group which may be substituted" as a substituent for the "amino group which may be substituted" represented by R, is exemplified by the same groups as those mentioned in the "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above. Said hydrocarbon group may have 1 to 3 optionally chosen substituents at any possible positions. Such substituents include lower alkyl groups which may be substituted, lower alkoxy groups which may be substituted, 25 aryl groups which may be substituted, lower cycloalkyl groups or lower cycloalkenyl groups which may be substituted, heterocyclic groups which may be substituted, carboxyl groups which may be esterified, carbamoyl groups which may be substituted, amino groups which may be substituted, hydroxyl groups which may be substituted, 30 thiol groups which may be substituted, acyl groups, 35

halogens (e.g., fluorine, chlorine, bromine), nitro, and cyano.

Such lower alkyl groups which may be substituted, lower alkoxy groups which may be substituted, aryl groups which may be substituted, lower cycloalkyl groups or lower cycloalkenyl groups which may be substituted, heterocyclic groups which may be substituted, carboxyl groups which may be esterified, carbamoyl groups which may be substituted, amino groups which may be substituted, hydroxyl groups which may be substituted, thiol groups which may be substituted, and acyl groups, are exemplified by the same substituents as those mentioned in the substituent in the "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above.

15

With respect to the formula (I) above, R is preferably an amino group which may be substituted by 1 or 2, preferably 1 substituent selected from the group consisting of (1) an acyl group selected from -COR<sup>1</sup>, -CSR<sup>2</sup>, -SO<sub>2</sub>R<sup>3</sup>, -SOR<sup>4</sup>, -CONHR<sup>5</sup> and -CSNHR<sup>6</sup> wherein each of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and R<sup>6</sup> is (1-1) a hydrogen atom; (1-2) a hydrocarbon group selected from the group consisting of: (a) an alkyl group having 1 to 10 carbon atom, (b) an alkenyl group having 2 to 10 carbon atoms, (c) an alkynyl group having 2 to 10 carbon atoms, (d) a cycloalkyl group having 3 to 12 carbon atoms, (e) a cycloalkenyl group having 5 to 12 carbon atoms, (f) a cycloalkadienyl group having 5 to 12 carbon atoms, (g) a C<sub>3-7</sub> cycloalkyl-C<sub>1-8</sub> alkyl group, (h) a C<sub>5-7</sub> cycloalkenyl-C<sub>1-8</sub> alkyl group, and (i) an aryl group having 6 to 10 carbon atoms, each of the substituents (a) to (i) may have 1 to 3 substituents selected from the group consisting of: (i) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of

halogen and a C<sub>1-3</sub> alkoxy group.

(ii) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

5 (iii) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

10 (iv) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

15 (v) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro.

20 (vi) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxygen carbonyl group or a (C<sub>7-10</sub> aralkyl)oxygen carbonyl group.

25 (vii) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro.

30 (viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of

halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group.

(ix) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

(ix-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

(ix-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

(ix-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

(ix-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

(ix-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro.

(ix-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub>

aralkyl)oxycarbonyl group,

5 (ix-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

10 (ix-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

15 (ix-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

20 (ix-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents

selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or 5 substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

10 (ix-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the 15 group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

12 (ix-12) halogen,

13 (ix-13) nitro, and

14 (ix-14) cyano.

(x) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said 20 C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, 25 and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

30 (x-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

35 (x-2) a C<sub>1-6</sub> alkoxy group which may be substituted by

1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

5 (x-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

10 (x-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

15 (x-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

20 (x-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

25 (x-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro.

30 (x-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen,

and nitro, or a cyclic amino group,

(x-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group.

(x-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

(x-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

- (x-12) halogen,
- (x-13) nitro, and
- (x-14) cyano,
- (xi) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,
- (xii) halogen,
- (xiii) nitro, and
- (xiv) cyano, or

(1-3) a heterocyclic group which may be substituted by 1 to 4 substituents selected from the group consisting of

- (i) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,
- (ii) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,
- (iii) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,
- (iv) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,
- (v) a heterocyclic group which may be substituted by

1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro.

5 (vi) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

10 (vii) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen, 15 and nitro,

20 (viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen, 25 and nitro, or a cyclic amino group,

30 (ix) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups 35 being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

(ix-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

5 (ix-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

10 (ix-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

15 (ix-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

20 (ix-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro.

(ix-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

25 (ix-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, 30 C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

35 (ix-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each

of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

(ix-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

(ix-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

(ix-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub>

aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

5 (ix-12) halogen,  
(ix-13) nitro, and  
(ix-14) cyano,

10 (x) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano,  
15 and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

20 (x-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

(x-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

25 (x-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

30 (x-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

35 (x-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen,

halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

5 (x-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

10 (x-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

15 (x-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

20 (x-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

35 (x-10) a thiol group which may be substituted by a

C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents 5 selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group 10 consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

(x-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted 15 or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

(x-12) halogen,  
(x-13) nitro, and  
25 (x-14) cyano,

(xi) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted 30 or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

- (xii) halogen,
- (xiii) nitro, and
- (xiv) cyano,

5 (2) an optionally esterified carboxyl group represented by the formula: -COOR<sup>7</sup> wherein R<sup>7</sup> is

- (2-1) a hydrogen atom;
- (2-2) a hydrocarbon group selected from the group consisting of:

10 (a) an alkyl group having 1 to 10 carbon atoms,

(b) an alkenyl group having 2 to 10 carbon atoms,

(c) an alkynyl group having 2 to 10 carbon atoms,

(d) a cycloalkyl group having 3 to 12 carbon atoms,

(e) a cycloalkenyl group having 5 to 12 carbon atoms,

15 (f) a cycloalkadienyl group having 5 to 12 carbon atoms,

(g) a C<sub>3-7</sub> cycloalkyl-C<sub>1-8</sub> alkyl group,

(h) a C<sub>5-7</sub> cycloalkenyl-C<sub>1-8</sub> alkyl group, and

(i) an aryl group having 6 to 10 carbon atoms, each of the substituents (a) to (i) may have 1 to 3 substituents selected from the group consisting of:

20 (i) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

(ii) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

25 (iii) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

(iv) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

30 (v) a heterocyclic group which may be substituted by

1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro.

5 (vi) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

10 (vii) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

15 (viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

20 (ix) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

(ix-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

5 (ix-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

10 (ix-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

15 (ix-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

20 (ix-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro.

25 (ix-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group.

30 (ix-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro.

35 (ix-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each

of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group.

(ix-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group.

(ix-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group.

(ix-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub>

aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group.

5 (ix-12) halogen,  
(ix-13) nitro, and  
(ix-14) cyano,

10 (x) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

15 (x-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

(x-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

20 (x-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

25 (x-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

30 (x-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen,

halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

5 (x-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxygen carbonyl group or a (C<sub>7-10</sub> aralkyl)oxygen carbonyl group,

(x-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

15 (x-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

25 (x-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

35 (x-10) a thiol group which may be substituted by a

C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

(x-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

(x-12) halogen,  
(x-13) nitro, and

(x-14) cyano,

(xi) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

(xii) halogen,

(xiii) nitro, and

(xiv) cyano, or

(2-3) a heterocyclic group which may be substituted by 1 to 4 substituents selected from the group consisting of

5 (i) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

10 (ii) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

(iii) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

15 (iv) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

20 (v) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

25 (vi) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

30 (vii) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

5 (viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

10 (ix) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

15 (ix-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

20 (ix-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

25 (ix-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

30 (ix-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

35 (ix-5) a heterocyclic group which may be substituted

by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro.

5 (ix-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

10 (ix-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro.

15 (ix-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group.

20 (ix-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group

and a C<sub>6-10</sub> aryl group,

(ix-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

(ix-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

(ix-12) halogen,

(ix-13) nitro, and

(ix-14) cyano,

(x) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or

substituted by 1 to 4 substituents selected from the group consisting of

5 (x-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

(x-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

10 (x-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

15 (x-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

20 (x-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

25 (x-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

30 (x-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

35 (x-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a

5       $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group and a  $C_{6-10}$  arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

10     (x-9) a hydroxyl group which may be substituted by a  $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group or a heterocyclic group, each of said  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{6-10}$  aryl and  $C_{7-12}$  aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a  $C_{1-4}$  alkoxy group, halogen, a  $C_{1-4}$  alkyl group and a  $C_{6-10}$  aryl group.

20     (x-10) a thiol group which may be substituted by a  $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group or a heterocyclic group, each of said  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{6-10}$  aryl and  $C_{7-12}$  aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a  $C_{1-4}$  alkoxy group, halogen, a  $C_{1-4}$  alkyl group and a  $C_{6-10}$  aryl group,

25     (x-11) an acyl group selected from the group consisting of formyl, a ( $C_{1-6}$  alkyl)carbonyl, a ( $C_{3-6}$  cycloalkyl)carbonyl, a ( $C_{6-10}$  aryl)carbonyl, a ( $C_{7-12}$  aralkyl)carbonyl, a ( $C_{1-6}$  alkyl)sulfinyl, a ( $C_{3-6}$  cycloalkyl)sulfinyl, a ( $C_{6-10}$  aryl)sulfinyl, a ( $C_{7-12}$

5 aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

(x-12) halogen,

(x-13) nitro, and

(x-14) cyano,

10 (xi) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

15 (xii) halogen,

(xiii) nitro, and

(xiv) cyano, and

20 (3) a hydrocarbon group selected from the group consisting of

25 (a) an alkyl group having 1 to 10 carbon atoms,

(b) an alkenyl group having 2 to 10 carbon atoms,

(c) an alkynyl group having 2 to 10 carbon atoms,

(d) a cycloalkyl group having 3 to 12 carbon atoms,

30 (e) a cycloalkenyl group having 5 to 12 carbon atoms,

(f) a cycloalkadienyl group having 5 to 12 carbon atoms,

(g) a C<sub>3-7</sub>, cycloalkyl-C<sub>1-8</sub> alkyl group,

(h) a C<sub>5-7</sub>, cycloalkenyl-C<sub>1-8</sub> alkyl group, and

(i) an aryl group having 6 to 10 carbon atoms,

35 each of the substituents (a) to (i) may have 1 to 3 substituents selected from the group consisting of:

(i) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

5 (ii) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

10 (iii) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

15 (iv) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

20 (v) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

(vi) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

25 (vii) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

30 (viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each

of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group.

5 (ix) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

10 (ix-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

15 (ix-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

20 (ix-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

25 (ix-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

30 (ix-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

(ix-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

(ix-7) a carbaomoyl group which may be substituted  
5 by 1 or 2 substituents selected from the group consisting  
of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl  
group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group,  
each of said groups being unsubstituted or substituted by  
10 1 to 5 substituents selected from the group consisting of  
halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by  
halogen, a C<sub>1-4</sub> alkyl group which may be substituted by  
halogen, and nitro,

(ix-8) an amino group which may be substituted by 1  
or 2 substituents selected from the group consisting of a  
15 C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group,  
a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each  
of said groups being unsubstituted or substituted by 1 to  
5 substituents selected from the group consisting of  
halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by  
20 halogen, a C<sub>1-4</sub> alkyl group which may be substituted by  
halogen, and nitro, or a cyclic amino group,

(ix-9) a hydroxyl group which may be substituted by  
a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group,  
a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said  
25 C<sub>1-6</sub> alkyl, a C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl  
groups being unsubstituted or substituted by 1 to 5  
substituents selected from the group consisting of halogen,  
a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a  
C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro,  
30 amino and cyano, and said heterocyclic group being  
unsubstituted or substituted by 1 to 3 substituents  
selected from the group consisting of a C<sub>1-4</sub> alkoxy group,  
halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group.

(ix-10) a thiol group which may be substituted by a  
35 C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group,  
a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said

5       $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{6-10}$  aryl and  $C_{7-12}$  aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a  $C_{1-4}$  alkoxy group, halogen, a  $C_{1-4}$  alkyl group and a  $C_{6-10}$  aryl group.

10     (ix-11) an acyl group selected from the group consisting of formyl, a ( $C_{1-6}$  alkyl)carbonyl, a ( $C_{3-6}$  cycloalkyl)carbonyl, a ( $C_{6-10}$  aryl)carbonyl, a ( $C_{7-12}$  aralkyl)carbonyl, a ( $C_{1-6}$  alkyl)sulfinyl, a ( $C_{3-6}$  cycloalkyl)sulfinyl, a ( $C_{6-10}$  aryl)sulfinyl, a ( $C_{7-12}$  aralkyl)sulfinyl, a ( $C_{1-6}$  alkyl)sulfonyl, a ( $C_{3-6}$  cycloalkyl)sulfonyl, a ( $C_{6-10}$  aryl)sulfonyl, a ( $C_{7-12}$  aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group and a  $C_{1-4}$  alkyl group.

15     (ix-12) halogen,  
         (ix-13) nitro, and  
         (ix-14) cyano.

20     (x) a thiol group which may be substituted by a  $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group or a heterocyclic group, each of said  $C_{1-6}$  alkyl,  $C_{3-6}$  cycloalkyl,  $C_{6-10}$  aryl and  $C_{7-12}$  aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

25     (x-1) a  $C_{1-6}$  alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of

halogen and a C<sub>1-3</sub> alkoxy group,

(x-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

5 (x-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

10 (x-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

15 (x-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

20 (x-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

25 (x-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

30 (x-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of

halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group.

(x-9) a hydroxyl group which may be substituted by 5 a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy 10 group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group 15 and a C<sub>6-10</sub> aryl group.

(x-10) a thiol group which may be substituted by a 20 C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy 25 group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group.

(x-11) an acyl group selected from the group 30 consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted 35 or substituted by 1 to 5 substituents selected from the

group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

(x-12) halogen,

(x-13) nitro, and

5 (x-14) cyano,

(xi) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

10 (xii) halogen,

(xiii) nitro, and

(xiv) cyano.

20 With respect to the formula (I) above, R is preferably a group represented by the formula:

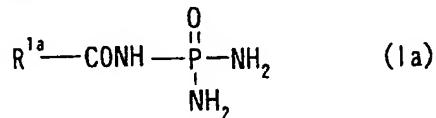
R<sup>1</sup>-CO-NH-

or

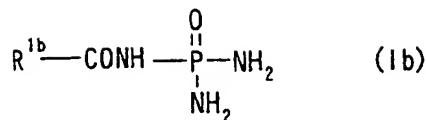
25 R<sup>3</sup>-SO<sub>2</sub>-NH-

wherein R<sup>1</sup> and R<sup>3</sup> have the same meanings as defined above, and the former (R<sup>1</sup>-CO-NH-) is more preferable.

Particularly preferred among the compound represented by the formula (I) is a compound represented by 30 the formula (Ia):



wherein R<sup>1a</sup> represents a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, or a compound represented by the formula (Ib):



wherein  $\text{R}^{1b}$  represents a non-cyclic hydrocarbon group substituted by (i) a cyclic hydrocarbon group which may be substituted, (ii) a heterocyclic group which may be substituted, (iii) hydroxyl group substituted by a cyclic hydrocarbon group which may be substituted, (iv) hydroxyl group substituted by a heterocyclic group which may be substituted, (v) thiol group substituted by a cyclic hydrocarbon group which may be substituted, or (vi) thiol group substituted by a heterocyclic group which may be substituted.

Namely,  $\text{R}^1$  is preferably  $\text{R}^{1a}$  or  $\text{R}^{1b}$ .  $\text{R}^1$  is more preferably  $\text{R}^{1a}$ .

With respect to the formula (Ia), the cyclic hydrocarbon group in the "cyclic hydrocarbon group which may be substituted" represented by  $\text{R}^{1a}$ , is exemplified by the saturated or unsaturated alicyclic hydrocarbon groups and aryl groups (aromatic hydrocarbon groups) mentioned to exemplify the hydrocarbon group in the "hydrocarbon group which may be substituted" represented by  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$  or  $\text{R}^6$  above, and preferable are  $\text{C}_{6-10}$  aryl groups such as phenyl, 1-naphthyl and 2-naphthyl.

With respect to the formula (Ia), the heterocyclic group in the "heterocyclic group which may be substituted" represented by  $\text{R}^{1a}$ , is exemplified by the same groups as those mentioned in the heterocyclic group in the "heterocyclic group which may be substituted" represented by  $\text{R}^1$ ,  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$  or  $\text{R}^6$  above, and preferable are aromatic heterocyclic groups such as thienyl (e.g., 2- or 3-thienyl), furyl (2- or 3-furyl), pyridyl (e.g., 2-pyridyl, 3-pyridyl, 4-pyridyl), azolyl [e.g., oxazolyl (e.g., 2-, 4- or 5-oxazolyl), isoxazolyl (e.g., 3-, 4- or 5-isoxazolyl)],

fused ring groups of thienyl or azolyl [e.g., benzothienyl (e.g., 2- or 3-benzo[b]thienyl), benzoxazolyl (e.g., 2-, 5- or 6-benz[d]oxazolyl), benzothiazolyl (e.g., 2-benzo[d]thiazolyl)] and fused furanyl groups [e.g., 5-benzofuranyl (e.g., 2- or 3-benzo[b]furanyl)], and 5-membered aromatic heterocyclic groups such as thienyl and furyl are more preferred.

The heterocyclic group in the "heterocyclic group which may be substituted" and the cyclic hydrocarbon group in the "cyclic hydrocarbon group which may be substituted" represented by  $R^{1a}$ , may have 1 to 3, preferably 1 to 2, optionally chosen substituents at any possible positions. These substituents are exemplified by the same groups as those mentioned in the substituent to the "heterocyclic group which may be substituted" represented by  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  or  $R^6$  above, and preferable are lower ( $C_{1-3}$ ) alkyl groups (e.g., methyl, ethyl, propyl, isopropyl, fluoromethyl, chloromethyl) which may be substituted by 1 to 3 halogens (e.g., fluorine, chlorine, bromine, iodine),  $C_{6-10}$  aryl groups (e.g., phenyl), lower ( $C_{1-3}$ ) alkoxy groups (e.g., methoxy, ethoxy, propoxy, isopropoxy, fluoromethoxy, chloromethoxy) which may be substituted by 1 to 3 halogens (e.g., fluorine, chlorine, bromine, iodine), halogens (e.g., fluorine, chlorine, bromine, iodine), nitro, cyano, ( $C_{1-6}$  alkyl)carbonyl groups and ( $C_{1-6}$  alkyl)sulfonyl groups.

The heterocyclic group which may be substituted for  $R^{1a}$ , is exemplified by a heterocyclic group which may have 1 to 4 substituents selected from the group consisting of: (i) a  $C_{1-6}$  alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a  $C_{1-3}$  alkoxy group, (ii) a  $C_{1-6}$  alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a  $C_{1-3}$  alkoxy group.

(iii) a  $C_{6-14}$  aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a  $C_{1-3}$  alkoxy group, halogen, a  $C_{1-3}$  alkyl group, amino, nitro and cyano,

5 (iv) a  $C_{3-7}$  cycloalkyl group or a  $C_{3-6}$  cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a  $C_{1-3}$  alkoxy group, halogen, a  $C_{1-3}$  alkyl group, amino, nitro and cyano,

10 (v) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, a  $C_{6-10}$  aryl group, and nitro,

15 (vi) a carboxyl group, a ( $C_{1-6}$  alkoxy)carbonyl group, a ( $C_{6-10}$  aryl)oxycarbonyl group or a ( $C_{7-10}$  aralkyl)oxycarbonyl group,

20 (vii) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a  $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group and a  $C_{6-10}$  arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, and nitro,

25 (viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a  $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group and a  $C_{6-10}$  arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

30 (ix) a hydroxyl group which may be substituted by a

C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents 5 selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group 10 consisting of

(ix-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

(ix-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 15 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

(ix-3) a C<sub>6-14</sub> aryl group which may be substituted by 20 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

(ix-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl 25 group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

(ix-5) a heterocyclic group which may be substituted by 30 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

(ix-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

(ix-7) a carbamoyl group which may be substituted by 35 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group,

a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

(ix-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

(ix-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, a C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

(ix-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or

substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group.

5 (ix-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group.

10 15 (ix-12) halogen,  
(ix-13) nitro, and  
(ix-14) cyano,

20 (x) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

25 30 (x-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

(x-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

35 (x-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of

a  $C_{1-3}$  alkoxy group, halogen, a  $C_{1-3}$  alkyl group, amino, nitro and cyano,

5 (x-4) a  $C_{3-7}$  cycloalkyl group or a  $C_{3-6}$  cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a  $C_{1-3}$  alkoxy group, halogen, a  $C_{1-3}$  alkyl group, amino, nitro and cyano.

10 (x-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a  $C_{1-4}$  alkoxy group which may be substituted by halogen, halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, a  $C_{6-10}$  aryl group, and nitro.

15 (x-6) a carboxyl group, a ( $C_{1-6}$  alkoxy)carbonyl group, a ( $C_{6-10}$  aryl)oxycarbonyl group or a ( $C_{7-10}$  aralkyl)oxycarbonyl group.

20 (x-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a  $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group and a  $C_{6-10}$  arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, and nitro.

25 (x-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a  $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group and a  $C_{6-10}$  arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a  $C_{1-4}$  alkoxy group which may be substituted by halogen, a  $C_{1-4}$  alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group.

30 (x-9) a hydroxyl group which may be substituted by a  $C_{1-6}$  alkyl group, a  $C_{3-6}$  cycloalkyl group, a  $C_{6-10}$  aryl group, a  $C_{7-12}$  aralkyl group or a heterocyclic group, each of said

C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

5 (x-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

10 (x-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

15 (x-12) halogen,

20 (x-13) nitro, and

25 (x-14) cyano,

30 (xi) an acyl group selected from the group consisting

of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group.

(xii) halogen,  
(xiii) nitro, and  
(xiv) cyano.

15 The cyclic hydrocarbon group which may be substituted for R<sup>1a</sup>, is exemplified by

- (a) a cycloalkyl group having 3 to 12 carbon atoms,
- (b) a cycloalkenyl group having 5 to 12 carbon atoms,
- (c) a cycloalkadienyl group having 5 to 12 carbon atoms,

20 or

- (d) an aryl group having 6 to 10 carbon atoms, each of which may have 1 to 3 substituents selected from the group consisting of:
  - (i) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,
  - (ii) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

25

- (iii) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,
- (iv) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub>

alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

5 (v) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro.

10 (vi) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group.

15 (vii) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro.

20 (viii) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group.

25 (ix) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano.

and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

5 (ix-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

(ix-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group,

10 (ix-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

15 (ix-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

20 (ix-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

25 (ix-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

30 (ix-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

35 (ix-8) an amino group which may be substituted by 1

or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group.

(ix-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, a C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group.

(ix-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group.

(ix-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub>

5       cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group.

10       (ix-12) halogen,  
         (ix-13) nitro, and  
         (ix-14) cyano,  
15       (x) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 4 substituents selected from the group consisting of

20       (x-1) a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

25       (x-2) a C<sub>1-6</sub> alkoxy group which may be substituted by 1 to 3 substituents selected from the group consisting of halogen and a C<sub>1-3</sub> alkoxy group.

30       (x-3) a C<sub>6-14</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano,

35       (x-4) a C<sub>3-7</sub> cycloalkyl group or a C<sub>3-6</sub> cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkoxy group, halogen, a C<sub>1-3</sub> alkyl group, amino, nitro and cyano.

5 (x-5) a heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, a C<sub>6-10</sub> aryl group, and nitro,

10 (x-6) a carboxyl group, a (C<sub>1-6</sub> alkoxy)carbonyl group, a (C<sub>6-10</sub> aryl)oxycarbonyl group or a (C<sub>7-10</sub> aralkyl)oxycarbonyl group,

15 (x-7) a carbamoyl group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro,

20 (x-8) an amino group which may be substituted by 1 or 2 substituents selected from the group consisting of a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group and a C<sub>6-10</sub> arylsulfonyl group, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, and nitro, or a cyclic amino group,

25 (x-9) a hydroxyl group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group

consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

5 (x-10) a thiol group which may be substituted by a C<sub>1-6</sub> alkyl group, a C<sub>3-6</sub> cycloalkyl group, a C<sub>6-10</sub> aryl group, a C<sub>7-12</sub> aralkyl group or a heterocyclic group, each of said C<sub>1-6</sub> alkyl, C<sub>3-6</sub> cycloalkyl, C<sub>6-10</sub> aryl and C<sub>7-12</sub> aralkyl groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group which may be substituted by halogen, a C<sub>1-4</sub> alkyl group which may be substituted by halogen, nitro, amino and cyano, and said heterocyclic group being unsubstituted or substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-4</sub> alkoxy group, halogen, a C<sub>1-4</sub> alkyl group and a C<sub>6-10</sub> aryl group,

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15 (x-11) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group,

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25 (x-12) halogen,

(x-13) nitro, and

(x-14) cyano,

(xi) an acyl group selected from the group consisting of formyl, a (C<sub>1-6</sub> alkyl)carbonyl, a (C<sub>3-6</sub> cycloalkyl)carbonyl, a (C<sub>6-10</sub> aryl)carbonyl, a (C<sub>7-12</sub> aralkyl)carbonyl, a (C<sub>1-6</sub> alkyl)sulfinyl, a (C<sub>3-6</sub> cycloalkyl)sulfinyl, a (C<sub>6-10</sub> aryl)sulfinyl, a (C<sub>7-12</sub> aralkyl)sulfinyl, a (C<sub>1-6</sub> alkyl)sulfonyl, a (C<sub>3-6</sub> cycloalkyl)sulfonyl, a (C<sub>6-10</sub> aryl)sulfonyl, and a (C<sub>7-12</sub> aralkyl)sulfonyl, each of said groups being unsubstituted

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or substituted by 1 to 5 substituents selected from the group consisting of halogen, a C<sub>1-4</sub> alkoxy group and a C<sub>1-4</sub> alkyl group.

- (xii) halogen,
- 5 (xiii) nitro, and
- (xiv) cyano.

With respect to the formula (Ia), R<sup>1a</sup> is preferably "an aromatic hydrocarbon group or an aromatic heterocyclic group, each of which may be substituted", more preferably "a 5-membered aromatic heterocyclic group which may be substituted". Examples of such groups include a thienyl group or a furyl group, each of which may be substituted by 1 to 3, preferably 1 or 2, substituents selected from the group consisting of a C<sub>1-3</sub> alkyl group which may be substituted by 1 to 3 halogen, a C<sub>1-3</sub> alkoxy group, halogen, nitro, cyano, a (C<sub>1-6</sub> alkyl)carbonyl, and (C<sub>1-6</sub> alkyl)sulfonyl, preferably a thienyl group which may be substituted by 1 or 2 C<sub>1-3</sub> alkyl groups or a furyl group which may be substituted by 1 or 2 C<sub>1-3</sub> alkyl groups.

R<sup>1a</sup> is particularly preferably a thienyl group or a furyl group each of which is substituted by 1 or 2 C<sub>1-3</sub> alkyl groups.

25 The non-cyclic hydrocarbon group in the "non-cyclic hydrocarbon group substituted by (i) a cyclic hydrocarbon group which may be substituted, (ii) a heterocyclic group which may be substituted, (iii) hydroxyl group substituted by a cyclic hydrocarbon group which may be substituted, (iv) 30 hydroxyl group substituted by a heterocyclic group which may be substituted, (v) thiol group substituted by a cyclic hydrocarbon group which may be substituted, or (vi) thiol group substituted by a heterocyclic group which may be substituted" represented by R<sup>1b</sup> above, is exemplified by 35 the saturated or unsaturated aliphatic chain hydrocarbon groups mentioned to exemplify the hydrocarbon group in the

"hydrocarbon group which may be substituted" represented by  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  or  $R^6$  above. Said non-cyclic hydrocarbon group has, at any possible positions, at least 1, preferably 1 or 2, of (i) a cyclic hydrocarbon group which may be substituted, (ii) a heterocyclic group which may be substituted, (iii) hydroxyl group substituted by a cyclic hydrocarbon group which may be substituted, (iv) hydroxyl group substituted by a heterocyclic group which may be substituted, (v) thiol group substituted by a cyclic hydrocarbon group which may be substituted, and/or (vi) thiol group substituted by a heterocyclic group which may be substituted.

Said "cyclic hydrocarbon group which may be substituted" (i) is exemplified by the "aryl groups which may be substituted" and the "lower cycloalkyl or lower cycloalkenyl groups which may be substituted" mentioned to exemplify the substituents of the hydrocarbon group in the "hydrocarbon group which may be substituted" represented by  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  or  $R^6$  above.

Said "heterocyclic group which may be substituted" (ii) is exemplified by the same groups as the "heterocyclic group which may be substituted" mentioned to exemplify the substituents in the "hydrocarbon group which may be substituted" represented by  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  or  $R^6$  above.

The cyclic hydrocarbon group in said "hydroxyl group substituted by a cyclic hydrocarbon group which may be substituted" (iii) and "thiol group substituted by a cyclic hydrocarbon group which may be substituted" (v) is exemplified by the saturated or unsaturated alicyclic hydrocarbon groups and aryl groups (aromatic hydrocarbon groups) mentioned to exemplify the hydrocarbon group in the "hydrocarbon group which may be substituted" represented by  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^5$  or  $R^6$  above.

The heterocyclic group in said "hydroxyl group substituted by a heterocyclic group which may be substituted" (iv) and "thiol group substituted by a

heterocyclic group which may be substituted" (vi) is exemplified by the same groups as the heterocyclic group mentioned to exemplify the "heterocyclic group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above.

5 Said "alicyclic hydrocarbon group" may have 1 to 5, preferably 1 to 3, optionally chosen substituents at any possible positions. Such substituents are exemplified by the same groups as those mentioned to exemplify the substituents of the hydrocarbon group in the "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above, and preferably exemplified by lower (C<sub>1-3</sub>) alkyl groups (e.g., methyl, ethyl, propyl, isopropyl, fluoromethyl, chloromethyl) which may be substituted by 1 to 3 halogens (e.g., fluorine, chlorine, bromine, iodine), lower (C<sub>1-3</sub>) alkoxy groups (e.g., methoxy, ethoxy, propoxy, isopropoxy, fluoromethoxy, chloromethoxy) which may be substituted by 1 to 3 halogens (e.g., fluorine, chlorine, bromine, iodine), halogens (e.g., fluorine, chlorine, bromine), nitro, amino and cyano.

10 20 Said "heterocyclic group" may have 1 to 4, preferably 1 to 3, optionally chosen substituents at any possible positions. Such substituents are exemplified by the same groups as those mentioned to exemplify the substituents of the heterocyclic group in the "heterocyclic group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above, and preferably exemplified by lower (C<sub>1-4</sub>) alkyl groups (e.g., methyl, ethyl, propyl, isopropyl), lower (C<sub>1-4</sub>) alkoxy groups (e.g., methoxy, ethoxy, propoxy, isopropoxy), halogens (e.g., fluorine, chlorine, bromine) and C<sub>6-10</sub> aryl groups (e.g., phenyl).

15 25 30 35 Said non-cyclic hydrocarbon group may have optionally chosen substituents at any possible positions, in addition to the above "cyclic hydrocarbon group which may be substituted", "heterocyclic group which may be substituted", and the like, but the total number of substituents in said non-cyclic hydrocarbon group is

5 preferably 1 to 3, more preferably 1 to 2. Such substituents are exemplified by the same groups as those mentioned in the substituent in the "hydrocarbon group which may be substituted" represented by R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> or R<sup>6</sup> above.

10 The cyclic hydrocarbon group in the "non-cyclic hydrocarbon group substituted by a cyclic hydrocarbon group which may be substituted" for R<sup>1b</sup>, is preferably exemplified by aryl groups (C<sub>1-4</sub> aryl groups such as phenyl, 1-naphthyl and 2-naphthyl), cycloalkyl groups having 3 to 7 carbon atoms, or cycloalkenyl groups having 3 to 6 carbon atoms. The cyclic hydrocarbon group may have 1 to 5, preferably 1 to 3, substituents. Such substituents are preferably exemplified by C<sub>1-3</sub> alkoxy groups, halogens, C<sub>1-3</sub> alkyl groups, amino, nitro and cyano.

15 R<sup>b</sup> is preferably a non-cyclic hydrocarbon group substituted by a heterocyclic group [e.g., an aromatic heterocyclic group such as thienyl (e.g., 2- or 3-thienyl), furyl (e.g., 2- or 3-furyl), azolyl [e.g., oxazolyl (e.g., 2-, 4- or 5-oxazolyl), isoxazolyl (e.g., 3-, 4- or 5-isoxazolyl)], fused ring groups of thienyl, furyl or azolyl isoxazolyl], benzothienyl (e.g., 2- or 3-benzo[b]thienyl), benzofuranyl (e.g., 2- or 3-benzo[b]furanyl), benzoxazolyl (e.g., 2-, 5- or 6-benz[d]oxazolyl), benzisoxazolyl (e.g., 3-, 4- or 5-benz[d]isoxazolyl), benzothiazolyl (e.g., 3-benzo[d]thiazolyl), benzimidazolyl (e.g., 1-benz[d]imidazolyl)] which may be substituted, more preferably a non-cyclic hydrocarbon group substituted by a thienyl or furyl group which may be substituted. Said non-cyclic hydrocarbon group is preferably exemplified by C<sub>1-10</sub> alkyl groups (preferably C<sub>1-3</sub> alkyl groups such as methyl, ethyl and propyl), C<sub>2-10</sub> alkenyl groups (preferably C<sub>2-4</sub> alkenyl groups such as ethenyl) and C<sub>2-10</sub> alkynyl groups (preferably C<sub>2-4</sub> alkynyl groups such as ethynyl). Said aromatic heterocyclic group may have 1 to 3 optionally

chosen substituents at any possible positions. Such substituents are preferably exemplified by lower ( $C_{1-3}$ ) alkyl groups (e.g., methyl, ethyl, propyl, isopropyl, fluoromethyl, chloromethyl) which may be substituted by 1 to 3 halogens (e.g., fluorine, chlorine, bromine, iodine),  $C_{6-10}$  aryl groups (e.g., phenyl), lower ( $C_{1-3}$ ) alkoxy groups (e.g., methoxy, ethoxy, propoxy, isopropoxy, fluoromethoxy, chloromethoxy) which may be substituted by 1 to 3 halogens (e.g., fluorine, chlorine, bromine, iodine), halogens (e.g., fluorine, chlorine, bromine, iodine), and nitro. The non-cyclic hydrocarbon group may have a substituent such as a cyano group in addition to the "cyclic hydrocarbon group which may be substituted", "heterocyclic group which may be substituted", and the like.

$R^b$  is preferably exemplified by (a)  $C_{1-10}$  alkyl groups, (b)  $C_{2-10}$  alkenyl groups and (c)  $C_{2-10}$  alkynyl groups, each of which may have 1 to 3 substituents selected from the group consisting of:

(i) a  $C_{6-14}$  aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a  $C_{1-3}$  alkoxy group, halogen, a  $C_{1-3}$  alkyl group, amino, nitro and cyano,

(ii) a  $C_{3-7}$  cycloalkyl group or a  $C_{3-6}$  cycloalkenyl group, each of which may be substituted by 1 to 5 substituents selected from the group consisting of a  $C_{1-3}$  alkoxy group, halogen, a  $C_{1-3}$  alkyl group, amino, nitro and cyano,

(iii) an aromatic heterocyclic group which may be substituted by 1 to 3 substituents selected from the group consisting of a  $C_{1-3}$  alkoxy group which may be substituted by halogen, halogen, a  $C_{1-3}$  alkyl group which may be substituted by halogen, a  $C_{6-10}$  aryl group, and nitro,

(iv) a hydroxyl group or a thiol group, each of which are substituted by a  $C_{3-6}$  cycloalkyl group which may be substituted by 1 to 5 substituents selected from the group

consisting of a C<sub>1-3</sub> alkyl group which may be substituted by halogen, a C<sub>1-3</sub> alkoxy group which may be substituted by halogen, halogen, nitro, amino and cyano,

5 (v) a hydroxyl group or a thiol group, each of which are substituted by a C<sub>6-10</sub> aryl group which may be substituted by 1 to 5 substituents selected from the group consisting of a C<sub>1-3</sub> alkyl group which may be substituted by halogen, a C<sub>1-3</sub> alkoxy group which may be substituted by halogen, halogen, nitro, amino and cyano, and

10 (vi) a hydroxyl group or a thiol group, each of which are substituted by a heterocyclic group which may be substituted by 1 to 4 substituents selected from the group consisting of a C<sub>1-4</sub> alkyl group, a C<sub>1-4</sub> alkoxy group, halogen, and a C<sub>6-10</sub> aryl group. Said C<sub>1-10</sub> alkyl groups, C<sub>2-10</sub> alkenyl groups and C<sub>2-10</sub> alkynyl groups may be substituted by further 15 1 cyano group.

In the present invention, the compound represented by the formula (I) or (Ia) is preferably exemplified by  
20 N-(diaminophosphinyl)-5-methyl-2-thiophenecarboxamide,  
N-(diaminophosphinyl)-2-methyl-3-furancarboxamide,  
N-(diaminophosphinyl)-5-methyl-3-furancarboxamide,  
N-(diaminophosphinyl)-3,5-dimethyl-2-furancarboxamide,  
and  
25 N-(diaminophosphinyl)-3,5-dimethyl-2-  
thiophenecarboxamide.

In the present invention, the salt of the compound represented by the formula (I), (Ia) or (Ib) is preferably a pharmaceutically acceptable salt, exemplified by salts formed with inorganic bases, salts formed with organic bases, salts formed with inorganic acids, salts formed with organic acids and salts formed with basic or acidic amino acids. Preferable salts formed with inorganic bases 30 include alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as calcium salt and 35

magnesium salt; and aluminum salt. Preferable salts formed with organic bases include ammonium salts and salts formed with trimethylamine, triethylamine, pyridine, picoline, ethanolamine, diethanolamine, triethanolamine, 5 dicyclohexylamine and N,N'-dibenzylethylenediamine. Preferable salts formed with inorganic acids include salts formed with hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid. Preferable salts formed with organic acids include salts formed with formic acid, acetic acid, trifluoroacetic acid, fumaric acid, 10 oxalic acid, tartaric acid, maleic acid, citric acid, succinic acid, malic acid, methanesulfonic acid, benzenesulfonic acid and p-toluenesulfonic acid. Preferable salts formed with basic amino acids include salts formed with arginine, lysine and ornithine. 15 Preferable salts formed with acidic amino acids include salts formed with aspartic acid and glutamic acid. These salts can be obtained by conventional methods.

Hydrates and non-hydrates of the compound 20 represented by the formula (I), (Ia) or (Ib) are included in the scope of the present invention.

The salt of the compound represented by the formula (II) or (III) below is exemplified by the same kinds of salts as those mentioned as the salt of the compound represented 25 by the formula (I) above.

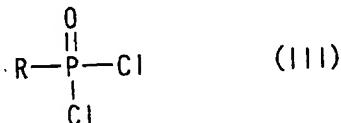
Production method for the compound represented by the formula (I) is hereinafter described. Both the compound represented by the formula (Ia) and the compound 30 represented by the formula (Ib) are within the scope of the formula (I).

The compound represented by the formula (I) can be produced by reacting a compound represented by the formula 35 (II):

R-H (II)

wherein the symbol has the same meanings as defined above, or a salt thereof, with phosphorus pentachloride, then reacting the resulting compound or a salt thereof with formic acid to yield a compound represented by the formula

5 (III):



wherein the symbol has the same meanings as defined above, or a salt thereof, and then reacting it with ammonia.

10 The desired compound can also be produced by reacting the compound represented by the formula (II) or a salt thereof with phosphorus oxychloride to yield the compound represented by the formula (III) or a salt thereof, and reacting it with ammonia.

15 In the reaction of the compound represented by the formula (II) or a salt thereof with phosphorus pentachloride or phosphorus oxychloride, any solvent can be used, as long as it does not interfere with the reaction, and such a solvent includes halogenated solvents such as carbon tetrachloride, chloroform, dichloromethane and 1,2-dichloroethane, ether solvents such as dioxane, tetrahydrofuran and diethyl ether, and hydrocarbon solvents such as benzene and toluene, and the reaction temperature is about -50 to 100 °C, preferably about -20 to 80 °C. The amount of phosphorus pentachloride or phosphorus oxychloride used is 0.5 to 10 mole equivalents, preferably 1 to 2 mole equivalents, per mole of the compound represented by the formula (II) or salt thereof. In the reaction with formic acid of the compound or its salt obtained by reacting the compound represented by the formula (II) or its salt with phosphorus pentachloride, halogenated solvents, ether solvents and hydrocarbon solvents as those mentioned above can be used. The reaction temperature is about -50 to 50 °C, preferably about 0 to 30 °C. The amount of formic acid used is 0.5 to 10 mole

equivalents, preferably 1 to 3 mole equivalents, per mole of the compound obtained by reacting the compound represented by the formula (II) or its salt with phosphorus pentachloride. In the reaction of the compound 5 represented by the formula (III) or its salt with ammonia, halogenated solvents, ether solvents and hydrocarbon solvents as those mentioned above can be used. The reaction temperature is about -50 to 50 °C, preferably about -20 to 10 °C.

10 The compound (I) or its salt may be isolated and purified by known separation and purification methods such as concentration, concentration under reduced pressure, distillation, fractional distillation, solvent extraction, chromatography, crystallization and recrystallization.

15 In the compounds or salts thereof to be used for the above reactions, a protecting group may be used for an amino group, carboxyl group or hydroxyl group not involved in the reaction. The addition and removal of the protecting group 20 can be achieved by known means.

25 Useful amino group-protecting groups include formyl, and C<sub>1-6</sub> alkylcarbonyl (e.g., acetyl, propionyl), phenylcarbonyl, C<sub>1-6</sub> alkyl-oxycarbonyl (e.g., methoxycarbonyl, ethoxycarbonyl), phenyloxycarbonyl, C<sub>7-10</sub> aralkyloxy-carbonyl (e.g., phenyl-C<sub>1-4</sub> alkyloxy-carbonyl such as benzyloxycarbonyl), trityl, phthaloyl and N,N-dimethylaminomethylene, each of which may have substituents. These substituents include halogen atoms (e.g., fluorine, chlorine, bromine, iodine), formyl, C<sub>1-6</sub> 30 alkyl-carbonyl (e.g., acetyl, propionyl, valeryl) and nitro groups, and the number of substituents is about 1 to 3.

35 Useful carboxyl group-protecting groups include C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl), phenyl, trityl and silyl, each of which may have substituents. These substituents include halogen

atoms (e.g., fluorine, chlorine, bromine, iodine), formyl, C<sub>1-6</sub> alkyl-carbonyls (e.g., acetyl, propionyl, valeryl) and nitro groups, and the number of substituents is about 1 to 3.

5       Useful hydroxyl group-protecting groups include C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl, isopropyl, butyl, tert-butyl), phenyl, C<sub>7-10</sub> aralkyl (e.g., phenyl-C<sub>1-4</sub> alkyl such as benzyl), formyl, C<sub>1-6</sub> alkyl-carbonyl (e.g., acetyl, propionyl), phenyloxycarbonyl, benzoyl, (C<sub>7-10</sub> 10 aralkyloxy)carbonyl (e.g., phenyl-C<sub>1-4</sub> alkyloxy-carbonyl such as benzyloxycarbonyl), pyranyl, furanyl and silyl, each of which may have substituents. These substituents include halogen atoms (e.g., fluorine, chlorine, bromine, iodine), C<sub>1-6</sub> alkyl (e.g., methyl, ethyl, propyl), phenyl, 15 C<sub>7-10</sub> aralkyl (e.g., phenyl-C<sub>1-4</sub> alkyl such as benzyl) and nitro groups, and the number of substituents is about 1 to 4.

20       Protecting groups can be removed by *per se* known methods or similar methods thereto, such as treatment with acid, base, reducing agent, ultraviolet rays, hydrazine, phenylhydrazine, sodium N-methyldithiocarbamate, tetrabutylammonium fluoride, palladium acetate etc.

25       The pharmaceutical composition of the present invention is a composition in which a acid-labile urease inhibitor has been stabilized, particularly a pharmaceutical composition in which the urease inhibitor has been stabilized in an oleaginous matrix. The present invention further provides a urease inhibitor-containing 30 gastrointestinal mucosa-adherent pharmaceutical composition including a viscogenic agent in its formulation to insure adhesion to the gastrointestinal mucosa.

35       Referring to oleaginous bases other than the polyglycerol fatty acid ester, any oleaginous substance having a melting point not below about 40°C, specifically within the range of about 40 to about 120°C, is generally

referred to by the term "lipid" in this specification. The term "stabilized in an oleaginous base" as used herein means the state in which the particular urease inhibitor has been dissolved or dispersed in an oleaginous base as well as the 5 state in which the urease inhibitor has been covered or coated with an oleaginous base.

When the composition is a gastrointestinal mucosa-adherent composition, it is adequate that the 10 composition contains a viscogenic agent therein or is coated with the coating material containing a viscogenic agent. That is to say that the present invention includes a pharmaceutical composition containing both an oleaginous base and a urease inhibitor, and which contains a viscogenic agent dispersed at least around the surface layer of the 15 composition.

It is also to be understood that inasmuch as the adhesion to the gastrointestinal mucosa is ensured by containing a viscogenic agent, the composition is referred to as being "gastrointestinal mucosa-adherent" even when 20 it is provided with a coating layer not containing a viscogenic

agent, e.g. an enteric coating layer or a gastric coating layer. The term "around the surface layer" is used to mean not only the very surface of the matrix but also the surface 25 region inclusive of the coating layer. The term "coating" is used herein to mean not only the process in which the entire surface of the particulate matrix is uniformly covered with a coating agent but also the process in which the surface of the matrix is partially covered.

Furthermore, when the oleaginous base or the coating 30 agent is a mixture, it may not exhibit a definite melting point but merely soften at a given temperature. In this specification, the term "melting point" is used to cover the softening point of such a mixture as well.

Referring to the oleaginous base for use in the 35 present invention, any oily substance that can be used as

a pharmaceutical oleaginous base can be employed. As such, the oleaginous base includes but is not limited to higher saturated fatty acids, fatty acid esters of alcohols (glycerol, polyglycerol, oils, hydrogenated oils, waxes, etc.), higher alcohols, phospholipids, sterols, sterol esters, and hydrocarbons. Particularly, fatty acid esters of alcohols are preferred.

Referring to said "fatty acid esters of alcohols", the "fatty acid" may for example be a monocarboxylic acid or a dicarboxylic acid. The dicarboxylic acid includes but is not limited to oxalic acid, malonic acid, succinic acid, glutaric acid, adipic acid, maleic acid, fumaric acid, phthalic acid, isophthalic acid, terephthalic acid, and sebamic acid. The monocarboxylic acid includes straight-chain saturated fatty acids such as acetic acid ( $C_2$ ), propionic acid ( $C_3$ ), butyric acid ( $C_4$ ), valeric acid ( $C_5$ ), caproic acid ( $C_6$ ), heptanoic acid ( $C_7$ ), caprylic acid ( $C_8$ ), nonanoic acid ( $C_9$ ), capric acid ( $C_{10}$ ), undecanoic acid ( $C_{11}$ ), lauric acid ( $C_{12}$ ), tridecanoic acid ( $C_{13}$ ), myristic acid ( $C_{14}$ ), pentadecanoic acid ( $C_{15}$ ), palmitic acid ( $C_{16}$ ), margaric acid ( $C_{17}$ ), stearic acid ( $C_{18}$ ), nonadecanoic acid ( $C_{19}$ ), arachic acid ( $C_{20}$ ), heneicosanoic acid ( $C_{21}$ ), behenic acid ( $C_{22}$ ), tricosanoic acid ( $C_{23}$ ), lignoceric acid ( $C_{24}$ ), etc.; straight-chain unsaturated fatty acids such as 10-undecenoic acid, 11-dodecenoic acid, 12-tridecenoic acid, trans-2-tetradecenoic acid, myristoleic acid, trans-9-tetradecenoic acid, 10-pentadecenoic acid, trans-2-hexadecenoic acid, palmitoleic acid, palmitoelaidic acid, 10-heptadecenoic acid, trans-10-heptadecenoic acid, trans-2-octadecenoic acid, petroselinic acid, petroelaidic acid, oleic acid, elaidic acid, cis-vaccenic acid, trans-vaccenic acid, linoleic acid, linoelaidic acid,  $\gamma$ -linolenic acid,  $\alpha$ -linolenic acid, 7-nonadecenoic acid, 10-nonadecenoic acid, trans-10-nonadecenoic acid, 10,13-nonadecadienoic acid, trans-10,trans-13-nonadecadienoic acid, 5-eicosenoic acid, 8-

eicosenoic acid, 11-eicosenoic acid, trans-11-eicosenoic acid, 11,14-eicosadienoic acid, 8,11-eicosadienoic acid, mead acid, homo- $\gamma$ -linolenic acid, 11,14,17-eicosatrienoic acid, 5,8,11-eicosatrienoic acid, arachidonic acid, 5 eicosatetraenoic acid, 5,8,11,14,17-eicosapentenoic acid (EPA), 12-heneicosenoic acid, erucic acid, brassidic acid, 13,16-docosadienoic acid, 13,16,19-docosatrienoic acid, 7,10,13,16-docosatetraenoic acid, 7,10,13,16,19-docosapentenoic acid, 7,10,13,16,19-docosahexenoic acid 10 (DHA), 14-tricosenoic acid, trans-14-tricosenoic acid, 15-tetracosenoic acid, etc.; branched fatty acids such as isolauric acid, 11-methylundecanoic acid, isomyristic acid, 13-methyltetradecanoic acid, isopalmitic acid, 15-methlyhexadecanoic acid, isostearic acid, 17-methyloctadecanoic acid, isoarachic acid, 19-methyleicosanoic acid, 9-methylundecanoic acid, 10-methyldodecanoic acid, 11-methyltridecanoic acid, 12-methyltetradecanoic acid, 13-methylpentadecanoic acid, 14-methylhexadecanoic acid, 15-methylheptadecanoic acid, 20 16-methyloctadecanoic acid, etc.; and hydroxy-fatty acids such as  $\beta$ -hydroxybutanoic acid,  $\gamma$ -hydroxybutanoic acid, 3-hydroxynonanoic acid, 2-hydroxydecanoic acid, 2-hydroxylauric acid, 2-hydroxytetradecanoic acid, 3-hydroxymyristic acid, 2-hydroxyhexadecanoic acid, 2-hydroxyoctadecanoic acid, 12-hydroxystearic acid, 2-hydroxyeicosanoic acid, 2-hydroxydocosanoic acid, 25 ricinoleic acid, ricinoelaidic acid, and so forth. Thus, fatty acids from C<sub>6</sub> to C<sub>40</sub> can be mentioned.

Preferred, among them, are straight-chain saturated or unsaturated fatty acids, with C8-C22 fatty acids being particularly suited for routine use.

The alcohol for use in said "fatty acid esters of alcohols" includes straight-chain or branched monohydric alcohols such as methyl alcohol, ethyl alcohol, n-propyl alcohol, n-butyl alcohol, n-pentyl alcohol, n-hexyl alcohol, n-heptyl alcohol, n-octyl alcohol, n-decyl

alcohol, n-lauryl alcohol, n-myristyl alcohol, n-cetyl alcohol, n-octadecyl alcohol, isopropyl alcohol, isobutyl alcohol, sec-butyl alcohol, tert-butyl alcohol, isopentyl alcohol, tert-pentyl alcohol, etc., dihydric alcohols such as ethylene glycol, propylene glycol, 1,3-propanediol, etc., and trihydric alcohols such as glycerol.

While the fatty acid alcohol ester is the ester of any of said fatty acids with an alcohol such as those mentioned above, saturated or unsaturated waxes and fatty acid glycerides (e.g. mono-, di-, and triacylglycerols) are particularly preferred. Those substances may be synthetic compounds or naturally-occurring substances. As to natural oils, waxes, etc., those composed of more than one fatty acid esters with or without other minor components such as free fatty acids and hydrocarbons can also be employed. Glycerol or polyglycerol fatty acid esters are particularly useful.

Referring to the "glycerol or polyglycerol fatty acid ester", the degree of polymerization of the polyglycerol is preferably about 2 to about 16 and more preferably about 2 to about 10.

The glycerol or polyglycerol fatty acid ester can be used alone or as a mixture of two or more species.

The preferred glycerol fatty acid ester is a fatty acid triglyceride (triacylglycerol) composed of 1 molecule of glycerol and 3 molecules of fatty acid. The fatty acid forming a di- or triacylglycerol may be of the same kind or different kinds. Here, preferred fatty acids are saturated fatty acids each containing about 4 to about 22 carbon atoms. Particularly preferred are saturated fatty acids of about 6 to about 18 carbon atoms.

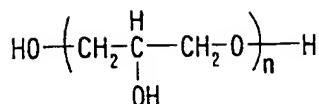
The above-mentioned "glycerol fatty acid ester" may be any of commercial products such as Miglyol 810 (caprylic/capric acid triglyceride, fatty acid composition = caprylic acid 65 to 75%, capric acid 25 to 35%), Miglyol 812 (caprylic/capric acid triglyceride, fatty acid

composition = caprylic acid 50 to 65%, capric acid 30 to 45%), Miglyol 829 (glycerol di(caprylate/caprate) succinate, fatty acid composition = caprylic acid 35 to 45%, capric acid 20 to 30%, succinic acid 12 to 16%), Miglyol 5 840 (propylene glycol dicaprylate, fatty acid composition = caprylic acid 65 to 80%, capric acid 15 to 30%), Dynasan 110 (capric acid triglyceride), Dynasan 112 (lauric acid triglyceride), Dynasan 114 (myristic acid triglyceride), Dynasan 116 (palmitic acid triglyceride), Dynasan 118 10 (stearic acid triglyceride) (all available from Huls Aktiengesellschaft, Germany), Panacete 800, Panacete 810, and Panacete 875 (all available from NOF Corporation), and Triester F-810 (caprylic/capric acid triglyceride) 15 (available from Nikko Chemicals (Tokyo)). Those glycerides can also be used in combination. Aside from the above-mentioned glycerides, the mono-, di-, and triglycerides of C<sub>14</sub>-C<sub>22</sub> saturated fatty acids (e.g. myristic acid, palmitic acid, stearic acid, behenic acid, etc.), for example 1-monostearin, 1-monopalmitin, etc.. 20 can also be employed.

25 The polyglycerol fatty acid ester may be any of a monoester, a diester, and a polyester. Polyglycerol fatty acid esters are not polymorphic crystallographically and do not substantially interact with the active ingredient so that even when they coexist with such active ingredient, the latter substances are substantially not deactivated but remain stable for an extended period of time.

30 Polyglycerol by definition is "a polyhydric alcohol containing n (cyclic) - (n+2) (straight-chain or branched) - hydroxyl groups and (n-1) (straight-chain or branched) - n (cyclic) ether bonds per molecule" [Polyglycerin Esters, (ed.) Sakamoto Yakuhin Kogyo Co., Ltd., published May 2, 1986, p12], and whichever of a straight-chain ester and a branched-chain ester can be used in the present invention.

35 For example, compounds of the following formula can be employed.



wherein n represents a degree of polymerization which is  
5 an integer of not less than 2. The value of n is generally  
about 2 to about 50, preferably about 2 to about 16, and  
for still better results, about 2 to about 10. The  
polyglycerol includes but is not limited to diglycerol,  
triglycerol, tetraglycerol, pentaglycerol, hexaglycerol,  
10 heptaglycerol, octaglycerol, nonaglycerol, decaglycerol,  
pentadecaglycerol, eicosaglycerol, and triacontaglycerol.  
Among those polyglycerols, tetraglycerol, hexaglycerol or  
decaglycerol is used in many cases.

The fatty acid includes saturated or unsaturated  
15 fatty acids each containing about 8 to about 40, preferably  
about 12 to about 25, and more preferably about 15 to about  
22 carbon atoms. The fatty acid thus includes but is not  
limited to palmitic acid, stearic acid, oleic acid,  
linoleic acid, linolenic acid, myristic acid, lauric acid,  
20 ricinoleic acid, caprylic acid, capric acid, and behenic  
acid. Among those fatty acids, stearic acid, oleic acid,  
lauric acid, linoleic acid, ricinoleic acid, and behenic  
acid are preferred.

The polyglycerol fatty acid ester includes but is not  
25 limited to behenic acid hexa(tetra)glyceride, caprylic  
acid mono(deca)glyceride, caprylic acid di(tri)glyceride,  
capric acid di(tri)glyceride, lauric acid  
mono(tetra)glyceride, lauric acid mono(hexa)glyceride,  
lauric acid mono(deca)glyceride, oleic acid  
30 mono(tetra)glyceride, oleic acid mono(hexa)glyceride,  
oleic acid mono(deca)glyceride, oleic acid  
di(tri)glyceride, oleic acid di(tetra)glyceride, oleic  
acid sesqui(deca)glyceride, oleic acid  
penta(tetra)glyceride, oleic acid penta(hexa)glyceride.

oleic acid deca(deca)glyceride, linoleic acid  
mono(hepta)glyceride, linoleic acid di(tri)glyceride,  
linoleic acid di(tetra)glyceride, linoleic acid  
di(hexa)glyceride, stearic acid mono(di)glyceride,  
5 stearic acid mono(tetra)glyceride, stearic acid  
mono(hexa)glyceride, stearic acid mono(deca)glyceride,  
stearic acid tri(tetra)glyceride, stearic acid  
tri(hexa)glyceride, stearic acid sesqui(hexa)glyceride,  
stearic acid penta(tetra)glyceride, stearic acid  
10 penta(hexa)glyceride, stearic acid deca(deca)glyceride,  
palmitic acid mono(tetra)glyceride, palmitic acid  
mono(hexa)glyceride, palmitic acid mono(deca)glyceride,  
palmitic acid tri(tetra)glyceride, palmitic acid  
tri(hexa)glyceride, palmitic acid sesqui(hexa)glyceride,  
15 palmitic acid penta(tetra)glyceride, palmitic acid  
penta(hexa)glyceride, palmitic acid deca(deca)glyceride  
and polyglycerol polyricinolate (e.g. tetraglycerol  
polyricinolate).

The preferred polyglycerol fatty acid ester includes  
20 behenic acid hexa(tetra)glyceride (e.g. Poem J-46B<sup>TM</sup>, Riken  
Vitamin Co.; HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.),  
stearic acid penta(tetra)glyceride (e.g. PS-310<sup>TM</sup>,  
Sakamoto Yakuhin Kogyo Co., Ltd.), stearic acid  
mono(tetra)glyceride (e.g. MS-310<sup>TM</sup>, Sakamoto Yakuhin  
25 Kogyo Co., Ltd.), stearic acid penta(hexa)glyceride (e.g.  
PS-500<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.), stearic acid  
sesqui(hexa)glyceride (e.g. SS-500<sup>TM</sup>, Sakamoto Yakuhin  
Kogyo Co., Ltd.), stearic acid deca(deca)glyceride (e.g.  
DAS-750<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.), stearic acid  
30 mono(hexa)glyceride (e.g. PO-500<sup>TM</sup>, Sakamoto Yakuhin Kogyo  
Co., Ltd.), oleic acid penta(tetra)glyceride (e.g. PO-310<sup>TM</sup>,  
Sakamoto Yakuhin Kogyo Co., Ltd.), oleic acid  
deca(deca)glyceride (e.g. DAO-750<sup>TM</sup>, Sakamoto Yakuhin  
Kogyo Co., Ltd.), stearic acid mono(deca)glyceride,  
35 polyglycerol polyricinolate (e.g. tetraglycerol  
polyricinolate (e.g. CRS-75<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co.,

Ltd.), and mixtures of such glycerides.

Those polyglycerol fatty acid esters can be used each alone or as a mixture of two or more species.

The molecular weight of the polyglycerol fatty acid ester is generally about 200 to about 5,000, preferably about 300 to about 3,000, more preferably about 2,000 to about 3,000. The hydrophile-lipophile balance (HLB) value of the polyglycerol fatty acid ester is generally about 1 to about 22, preferably about 1 to about 15, more preferably about 1 to about 9 and for still better results, about 1 to about 4. Two or more polyglycerol fatty acid esters differing in HLB value from each other may be used in combination to provide for the necessary HLB value. By adjusting the HLB value of the polyglycerol fatty acid ester judiciously, the dissolution and release kinetics of the active substance can be controlled.

A suitable polyglycerol fatty acid ester is selected according to the species of active ingredient used and the intended dosage form. Generally, polyglycerols with degrees of polymerization in the range of about 2 to about 16 are preferred. The particularly preferred range is about 2 to about 10. Preferred are esters such that the fatty acid has formed an ester bond with at least one of the (degree of polymerization +2) hydroxyl groups, preferably such that the fatty acid or acids have formed ester bonds with not less than 60%, more preferably not less than about 80%, of the total number of hydroxyl groups in the polyglycerol. The fatty acid or acids are preferably saturated acids each containing about 6 to about 22, preferably about 8 to about 18 carbon atoms. The fatty acid involved in the formation of the ester bonds may be of the same kind or different kinds.

When the composition is designed to be adherent to the gastrointestinal mucosa, the polyglycerol fatty acid ester should also be selected with reference to the type of viscogenic agent to be employed. Preferably, those

esters which are solid at atmospheric temperature (ca 15°C) are employed. The melting point of the polyglycerol fatty acid ester may for example be about about 15 to about 80°C, preferably about 30 to about 75°C, and for still better 5 results, about 45 to about 75°C. A gastrointestinal mucosa-adherent composition according to the present invention may be produced by using a mixture of two or more different polyglycerol fatty acid esters and in such a case a liquid polyglycerin fatty acid ester may be included in 10 the mixture if the final matrix is solid at atmospheric temperature.

The "polyglycerol fatty acid ester" which can be used with advantage in the above application can also be procured from commercial sources. For example, PS-310, MS-310, 15 HB-310, PO-310, PO-500, DAO-750, DAS-750, etc. are available from Sakamoto Yakuhin Kogyo Co., Ltd. (Osaka), Poem J 46B from Riken Vitamin (Tokyo), and Tetraglyn 5-S (tetraglycerol pentastearate), Decaglyn 10-S (decaglycerol decastearate), etc. from Nikko Chemicals 20 (Tokyo).

Those esters can be used each alone or as a mixture of two or more species. Moreover, they can be used in combination with glycerol fatty acid esters and/or other oleaginous bases.

25 The "oil" mentioned above includes but is not limited to soybean oil, olive oil, rapeseed oil, peppermint oil, sesame oil, castor oil, tsubaki oil, wheat germ oil, fennel oil, corn oil, sunflower oil, cottonseed oil, coconut oil, peanut oil, etc., the corresponding hydrogenated oils, beef tallow, and lard. Among those oils and fats, hydrogenated 30 cottonseed oil, hydrogenated castor oil (e.g. Lubriwax<sup>TM</sup>, Freund Industrial), and hydrogenated soybean oil are preferred.

35 The "wax" mentioned above includes but is not limited to carnauba wax, sperm wax, beeswax, and white Japan wax.

The "higher saturated fatty acid" mentioned above

includes C<sub>8-22</sub> fatty acids, inclusive of salts thereof, among the fatty acids mentioned hereinbefore, such as caprylic acid, capric acid, palmitic acid, stearic acid, and behenic acid etc.

5 The "higher alcohol" mentioned above includes but is not limited to C<sub>10-20</sub> alcohols such as cetyl alcohol and stearyl alcohol.

The "phospholipid" mentioned above may for example be hydrogenated lecithin.

10 The "sterol or its ester" mentioned above includes but is not limited to cholesterol,  $\alpha$ -cholestane,  $\beta$ -cholestanol, epicoprostanol, demosterol, fucosterol, lanosterol, ergosterol,  $\beta$ -sitosterol, esters of cholesterol with C<sub>2-24</sub> saturated fatty acids, and esters of cholesterol with C<sub>14-24</sub> unsaturated (the number of double bonds 1-6) fatty acids.

15 The "hydrocarbon" mentioned above includes but is not limited to paraffin and microcrystalline wax.

20 The above-mentioned oleaginous bases can be used each alone or in combination.

25 In consideration of the stability of the active ingredient and the absorption kinetics of oral preparation, the above-mentioned glycerol or polyglycerol fatty acid esters and waxes are most generally chosen as the oleaginous base in the practice of the invention.

30 The pharmaceutical composition according to the present invention is a composition for oral administration in which the active ingredient has been stabilized. This "pharmaceutical composition" may be liquid or solid, and can be produced by analogue to the per se known technology. The following is a typical production process.

35 When an oleaginous base which is liquid at atmospheric temperature (about 5 to about 30°C) is employed, the active ingredient is added and dispersed therein with agitation to provide the objective composition.

When an oleaginous base which is solid at atmospheric

temperature (about 5 to about 30°C) is employed, it is melted or otherwise liquefied and after the active ingredient is dispersed therein, the dispersion is solidified. For example, the oleaginous base is heated to a temperature 5 close to or beyond its melting point and the active ingredient is dissolved or dispersed in the liquefied base in the per se known manner. This solution or dispersion is then solidified by cooling. In the course of solidification, the solution or dispersion may be molded 10 into particles or pellets. The per se known molding techniques can be employed for this purpose. When powders are desired, spherical particles with a diameter of about 0.1 to about 1,000 µm are manufactured. The molding technology includes the spray drying process which 15 comprises spraying said solution or dispersion containing the active ingredient in a hot air current and the spray chilling process in which oil droplets are prepared and rapidly chilled.

The proportion of the oleaginous base relative to the 20 total weight of the composition is generally about 5 to about 98 weight %, preferably about 20 to about 95%, more preferably about 40 to about 95% and to the active ingredient in the composition may, for example, be about 0.01 to about 15,000 times by weight, preferably about 0.1 to about 1,000 times by weight, and for still better result, 25 about 0.1 to about 100 times by weight. However, insofar as the active ingredient can be completely covered with the oleaginous base, the above range need not be strictly adhered to.

The concentration or content of the active ingredient 30 in the composition can be judiciously selected according to the physicochemical properties of the composition. When the composition is a liquid, the concentration of the active ingredient may be about 0.01 to about 200% (w/v), 35 preferably about 0.1 to about 100% (w/v). When the composition is a solid preparation, the content of the

active ingredient may be about 0.01 to about 95% (w/w), preferably about 0.1 to about 50% (w/w), and more preferably about 5 to about 50% (w/w).

In addition, where necessary, preservatives (e.g. 5 benzyl alcohol, ethyl alcohol, benzalkonium chloride, phenol, chlorobutanol, etc.), antioxidants (e.g. 2-t-butyl-4-hydroxyanisole, propyl gallate, ascorbyl palmitate, a-tocopherol, etc.), thickeners (e.g. lecithin, hydroxypropylcellulose, aluminum stearate, etc.), and 10 other additives can be incorporated.

When the pharmaceutical composition of the invention is to be embodied as a urease inhibitor-containing 15 gastrointestinal mucosa-adherent preparation, the composition may be processed into any preparation that will adhere to the mucosa in the target region of the gastrointestinal tract, stays long within the tract, and/or promotes absorption of the active ingredient in the absorption site. The preferred preparation includes a matrix. The matrix is preferably prepared using said 20 polyglycerol fatty acid ester. For example, it may be a gastrointestinal mucosa-adherent matrix comprising said polyglycerol fatty acid ester and said viscogenic agent. It may also be a gastrointestinal mucosa-adherent matrix comprising said lipid, which is described in detail below, 25 and said viscogenic agent. The still more preferred matrix is a matrix comprising said polyglycerol fatty acid ester, lipid, and viscogenic agent. The gastrointestinal mucosa-adherent matrix is preferably a matrix in which said 30 viscogenic agent has been dispersed in said polyglycerol fatty acid ester and/or lipid or a matrix comprising said polyglycerol fatty acid ester and/or lipid as coated with said viscogenic agent. The melting point of such a gastrointestinal mucosa-adherent matrix may for example be about 30 to about 120°C, preferably about 40 to about 120°C.

35 The lipid, among said oleaginous bases, is one having a melting point of about 40 to about 120°C, preferably about

40 about to 95°C. The lipid includes but is not limited to saturated fatty acids of about 14 to about 22 carbon atoms (e.g. myristic acid, palmitic acid, stearic acid, behenic acid, etc.) or their salts (sodium salts, potassium salts, etc.); higher alcohols of about 16 to about 22 carbon atoms (e.g. cetyl alcohol, stearyl alcohol, etc.); fatty acid glycerol esters such as the monoglycerides, diglycerides, triglycerides, etc. of the above-mentioned fatty acids (e.g. 1-monostearin, 1-monopalmitin, etc.); oils (e.g. castor oil, cottonseed oil, soybean oil, rapeseed oil, beef tallow, etc., inclusive of the corresponding hydrogenated oils); waxes (e.g. beeswax, carnauba wax, sperm wax, etc.); hydrocarbons (e.g. paraffin, microcrystalline wax, etc.); and phospholipids (e.g. hydrogenated lecithin etc.).

5 Preferred, among those lipids, are oils, waxes, C<sub>14-22</sub> saturated fatty acids, higher(C<sub>16-22</sub>) alcohols, and hydrocarbons. The more preferred lipids are hydrogenated cottonseed oil, hydrogenated castor oil, hydrogenated soybean oil, carnauba wax, stearic acid, stearyl alcohol,

10 and microcrystalline wax.

15 20

A agent capable of being viscous with water, (viscogenic agent) is not particularly restricted in kind as long as it becomes sufficiently viscous with water to attach itself to the gastrointestinal mucosa and is pharmaceutically acceptable. Preferred, however, are those agents which are markedly swollen by water and develop high degrees of viscosity. The viscogenic agent, thus, includes synthetic polymers and naturally-occurring viscogenic materials. The preferred polymer is a polymer such that the viscosity of a 2% aqueous solution thereof at 20°C is about 3 to about 50,000 cps., preferably about 10 to about 30,000 cps., and for still better results, about 15 to about 30,000 cps. However, when a polymer which gains in viscosity on neutralization is used, the preferred 25 30 35 polymer is such that the viscosity of a 0.2% solution after neutralization at 20°C is about 100 to about 500,000 cps.

preferably about 100 to about 200,000 cps, and for still better results, about 1,500 to about 100,000 cps.

The value of the viscosity is measured with a Brookfield viscometer.

5 Preferably, the above-mentioned polymer is an acidic polymer which includes but is limited to carboxyl- or sulfo-containing polymers and the corresponding salt-containing polymers. Particularly preferred are carboxyl-containing polymers and carboxylate salt-containing polymers.

10 The carboxyl (inclusive of its salt)-containing polymer is preferably an acrylic homopolymer or copolymer containing acrylic acid as a monomer unit or a salt thereof. The salt includes monovalent metal salts such as the sodium salt, potassium salt, etc. and divalent metal salts such as the magnesium salt, calcium salt, etc. and ammonium salt and so on. The acrylic polymer, inclusive of its salt, includes polymers containing carboxyl groups in a proportion of about 58 to about 63 weight % and having a molecular weight of about  $20 \times 10^4$  to about  $600 \times 10^4$ , and preferably about  $100 \times 10^4$  to about  $500 \times 10^4$ . The preferred acrylic polymer, inclusive of its salt, includes acrylic acid homopolymers and their salts (sodium, ammonium, calcium and so on). Such polymers are listed under the heading of carboxyvinyl polymer in Japanese Standards of 15 20 25 Pharmaceutical Ingredients (October 1986).

As specific examples of said polymer, there can be mentioned carbomer [Carbopol, the trademark of The B. F. Goodrich Company] 940, 934, 934P, 940, 941, 974P, 971P, 1342 30 (NF XVII), EX214 etc. (hereinafter referred to as carbopol), HIVISWAKO<sup>TM</sup> 103, 104, 105, 204 and (Wako Pure Chemical Industries), NOVEON AA1<sup>TM</sup> (The B. F. Goodrich Company), and calcium polycarbophil (USP XXII).

35 The naturally-occurring viscoelastic agent includes but is not limited to mucin, agar, gelatin, pectin, carrageenin, sodium alginate, locust bean gum, xanthan gum,

tragacanth gum, gum arabic, chitosan, pullulan, curdlan, waxy starch, sucralfate, and cellulose and its derivatives (e.g. cellulose sulfate).

5 The most preferred viscogenic agent is an acrylic polymer or its salt in the present invention.

These viscogenic agents can be used alone or in combination.

Referring to the amount of the viscogenic agent, its amount in the gastrointestinal mucosa-adherent composition 10 may for example be about 0.005 to about 99 weight %, preferably about 0.5 to about 45 weight %, more preferably about 1 to about 30 weight %, furthermore preferably about 1 to about 25 weight %, and for the still better result, about 1 to about 20 %. When, for example, the viscogenic 15 agent is dispersed in a composition comprising the polyglycerol fatty acid ester or the lipid, the amount of the viscogenic agent is about 0.005 to about 95 weight %, preferably about 0.5 to about 30 weight %, more preferably about 1 to about 25 weight %, and for the still better result, 20 about 1 to about 20 weight % based on the total weight of the composition. When the viscogenic agent is dispersed in the coating material of the composition comprising the polyglycerol fatty acid ester or the lipid, the proportion 25 of the viscogenic agent is also about 0.005 to about 95 weight %, preferably about 0.5 to about 30 weight %, more preferably about 1 to about 25 weight %, and for the still better result, about 1 to about 20 weight % based on the total composition.

When the gastrointestinal mucosa-adherent matrix is 30 a matrix comprising said polyglycerol fatty acid ester and the viscogenic agent or a matrix comprising said lipid and the viscogenic agent, the amount of the polyglycerol fatty acid ester or the lipid is about 5 to about 98 weight %, preferably about 20 to about 95 weight %, and more 35 preferably about 40 to about 95 weight % based on the total weight. And the proportion of the polyglycerol fatty acid

ester or the lipid relative to the active ingredient is about 0.01 to about 15,000 parts by weight, preferably about 0.1 about to 1,000 parts by weight, and more preferably about 0.1 to about 100 parts by weight.

5        The matrix prepared by using said polyglycerol fatty acid ester may be supplemented with said lipid. The lipid which can be used is a pharmaceutically acceptable water-insoluble substance which is capable of regulating the rate of release of the active ingredient, and the 10 specific lipids mentioned hereinbefore, for instance, can be employed.

When the lipid and the polyglycerol fatty acid ester are used together, the amount of the polyglycerol fatty acid ester and the lipid together is about 5 to about 98 weight %, 15 preferably about 20 to about 95 weight %, more preferably about 40 to about 95 weight % based on the total weight. And the amount of the lipid should be within the range not detracting from the adhesion of the composition to the 20 gastrointestinal mucosa, and may range from about 0.01 to about 15,000 parts by weight, preferably about 0.1 about to 1,000 parts by weight, more preferably about 0.1 to about 100 parts by weight, relative to the active ingredient.

25        The liquid or solid pharmaceutical composition of the invention can be administered orally either as it is or as formulated into a preparation which can be manufactured by the established pharmaceutical procedures. The liquid composition can be directly administered via a gastric catheter or a feeding tube or in the form of a hard or soft capsule. The solid composition can be administered orally 30 in the bulk form, as encapsulated, or in the form of a tablet.

35        Preparations containing the pharmaceutical composition of the invention can be manufactured by basically following the per se known procedures as such or as modified. Moreover, in the manufacture of the oral preparation, a variety of additives which are conventionally formulated in an oral preparation can be

added for controlling the rate of release of the active ingredient or to meet other pharmaceutical needs. Among such additives are excipients (e.g. lactose, corn starch, talc, crystalline cellulose, powdered sucrose, magnesium stearate, mannitol, light silicic anhydride, magnesium carbonate, calcium carbonate, L-cysteine, etc.); binders (e.g. starch, sucrose, gelatin, gum arabic powder, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, pullulan, dextrin, etc.); disintegrators (e.g. carboxymethylcellulose calcium, low-substituted hydroxypropylcellulose, croscarmellose sodium, etc.); anionic surfactants (e.g. sodium alkylsulfonates etc.) and nonionic surfactants (e.g. polyethoxylated sorbitan fatty acid esters, polyethoxylated fatty acid esters, polyethoxylated castor oil derivatives, etc.); antacids and mucosal protectants (e.g. magnesium hydroxide, magnesium oxide, aluminium hydroxide, aluminium sulfate, magnesium aluminometasilicate, magnesium aluminosilicate, sucralfate, etc.); cyclodextrins and cyclodextrincarboxylic acids (e.g. maltosyl-*b*-cyclodextrin and maltosyl-*b*-cyclodextrincarboxylic acid); coloring agents; corrigents; adsorbents; antiseptics; lubricants; antistatic agents; and disintegration retardants. The levels of addition of those additives can be respectively selected from the range not detracting from the stability and efficiency of absorption of the active substance.

When, for example, a liquid pharmaceutical composition of the invention is processed into soft capsules, various known forms can be adopted. Thus, the geometry, size, and formulation of the capsule and the manufacturing method can be freely selected. The capsule may for example be spherical, oval, oblong, tubular, spindle-shaped, self-cut, duplex, square, or heart-shaped.

The capsule size is generally selected from the range of about 1 mg to about 10 g in terms of capacity.

The commonest film material that can be used is a mixture of gelatin (e.g. alkalinized gelatin) and a 5 suitable plasticizer, optionally supplemented with a coloring agent, an antiseptic, a flavor, and/or a corrigent.

The capsule manufacturing technology that can be utilized includes the plate method, rotary die method, and 10 seamless method, although the rotary die method is preferred.

The solid pharmaceutical composition of the present invention, either as such or as a uniform mixture of the composition and said additives, can be processed into hard 15 capsules using hard capsule shells. As such capsule shells, hard gelatin capsule shells having capacities within the range of about 0.13 to about 1.37 ml are generally used and the filling operation can be carried out by means of a disk-type, compress-type, or Auger type filling machine. 20 Tablets can be manufactured by compressing a powdery mixture containing the pharmaceutical composition of the invention. The tablet shape and size can be freely selected. For example, ellipsoidal, football-shaped, heart-shaped, and other tablets can be provided, with or without a 25 dividing line. The tablet machine may be an eccentric machine or a rotary machine.

The pharmaceutical composition of the present invention can be coated with an enteric coating material to provide an enteric preparation. The "enteric coating 30 material" means an enteric polymer which is substantially insoluble in the acidic region of pH but at least partially soluble in the weakly acidic to basic region. The term "acid region" is used herein to mean the range of pH about 0.5 to about 4.5, preferably pH about 1.0 to about 2.0. The 35 "weakly acidic to basic region" means the range of pH about 5.0 to about 9.0, preferably pH about 6.0 to about 7.5. As

specific examples of said enteric coating material, there can be mentioned cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxypropylmethyl acetate succinate (Shin-Etsu Chemicals), methacrylic acid copolymers (Eudragit<sup>TM</sup> L-30D-55, L100-55, L100, S100, etc., Röhm-Pharma), among others. Those materials can be safely used as they are in enteric preparation.

The coating technology that can be used includes a variety of per se known methods, such as pan coating, fluidized-bed coating, roll coating, and so on. When the coating material is a solution or dispersion containing water or an organic solvent, the spray coating method can also be employed. The proportion of said water or organic solvent may for example be about 25 to about 99 weight %. There is no particular limitation on the kind of said organic solvent. Thus, for example, alcohols (e.g. methanol, ethanol, isopropyl alcohol, etc.); ketones (e.g. acetone etc.); and halogenated hydrocarbons (e.g. chloroform, dichloromethane, trichloromethane, etc) can be mentioned.

The above-mentioned gastrointestinal mucosa-adherent composition can be used as it is or as processed into gastrointestinal mucosa-adherent preparations.

Furthermore, various additives conventionally incorporated in solid preparations (e.g fine granules, granules, etc.) can be added to the preparation form as well unless they cause an adverse influence. Among such additives are various excipients such as lactose, corn starch, talc, crystalline cellulose (e.g. Avicel), powdered sucrose, magnesium stearate, mannitol, light silicic anhydride, magnesium carbonate, calcium carbonate, L-cysteine, etc.; binders such as starch, sucrose, gelatin, powdered gum arabic, methylcellulose, carboxymethylcellulose, carboxymethylcellulose sodium, hydroxypropylcellulose, hydroxypropylmethylcellulose,

polyvinylpyrrolidone, pullulan, dextrin, etc.; disintegrators such as carboxymethylcellulose calcium, low-substituted hydroxypropylcellulose, croscarmellose sodium, carboxymethylstarch sodium, hydroxypropylstarch, 5 partially dextrinized starch, etc.; anionic surfactants such as sodium alkylsulfonates etc. and nonionic surfactants such as polyethoxylated sorbitan fatty acid esters, polyethoxylated fatty acid esters, polyethoxylated castor oil derivatives, etc.; antacids and mucosal 10 protectants such as magnesium hydroxide, magnesium oxide, aluminium hydroxide, aluminium sulfate, magnesium aluminometasilicate, magnesium aluminosilicate, sucralfate, etc.; coloring agents; corrigents; adsorbents; antiseptics; lubricants; antistatics; and disintegration 15 retardants. The levels of addition of those additives can be respectively selected from the range not detracting from adhesion of the composition to the mucosa.

The gastrointestinal mucosa-adherent solid 20 composition comprising said viscoagent dispersed in a matrix comprising a polyglycerol fatty acid ester and/or lipid may be any dispersion of said polyglycerol fatty acid ester and/or lipid, viscoagent, and active ingredient. Dispersion can be effected by the per se known technology.

The gastrointestinal mucosa-adherent solid 25 composition can be produced by the analogue to the per se known pharmaceutical procedures. A typical process comprises melting the polyglycerol fatty acid ester and/or lipid at a temperature beyond its melting point, adding said viscoagent and said active ingredient to the melt, either together or serially to thereby disperse them in the 30 melt, and cooling the dispersion. The heating temperature may for example be about 40 to about 150°C, preferably about 50 to about 110°C, and more preferably about 50 to about 90°C. This process can be carried out using a conventional 35 granulating machine and the composition is preferably molded into solid beads (e.g. fine granules etc.) by a spray

granulation technique, for example spray chilling.

The spray chilling method typically comprises dripping a mixed dispersion of the viscogenic agent and active ingredient in a molten polyglycerol fatty acid ester and/or lipid at a constant flow rate onto a rotary disk revolving at a high speed of, for example, about 10 to about 6,000 rpm, preferably about 900 to about 6,000 rpm, more preferably about 1,000 to about 5,000 rpm, furthermore preferably about 2,500 to about 3,000 rpm. The rotary disk 5 may for example be a flat, smooth disk, typically made of aluminum and measuring about 5 to about 100 cm in diameter, preferably about 10 to about 20 cm in diameter. The dripping rate of said molten dispersion can be selected 10 according to the designed particle diameter and is generally about 1 to about 1,000 g/min., preferably about 2 to about 200 g/min., and more preferably about 5 about 15 to 100 g/min. The granules thus obtained are substantially spherical so that a uniform film can be formed on their surface with good efficiency in the subsequent coating 20 step.

When the gastrointestinal mucosa-adherent composition according to the invention is manufactured by the above method, it is possible not only to render the product adherent but also to stabilize the urease inhibitor 25 in the preparation.

An alternative production process comprises kneading the viscogenic agent and active ingredient into the polyglycerol fatty acid ester and/or lipid, and granulating the resulting dispersion. The solvent for use in this 30 process may be a solvent of the common variety (e.g. methanol, acetonitrile, chloroform, etc.).

A further alternative process for producing said solid composition comprises the use of melt granulation technology. A typical melt granulation process comprises 35 heating the polyglycerol fatty acid ester and/or lipid at a temperature near its melting point, for example a

temperature ranging from its melting point to a temperature about 5°C below the melting point, subjecting the resulting melt to granulation, such as the above-mentioned spray chilling, and floating the resulting fine particles 5 together with the viscogenic agent and active ingredient under moderate heating at a suitable temperature to provide an gastrointestinal mucosa-adherent matrix. In this process, the influence of heat on the active ingredient can be mitigated. Therefore, even when the active ingredient 10 is a peptide or a protein, a solid composition can be manufactured without the risk of deactivation of the active ingredient.

The solid composition comprising a matrix made up of a polyglycerol fatty acid ester and/or a lipid and being 15 coated with a viscogenic agent may be one coated with a viscogenic agent as such or preferably one coated with a coating material containing a viscogenic agent. The coating material may be a composition containing at least one member selected from the class consisting of said 20 polyglycerol fatty acid ester, said lipid, and said water-insoluble polymer in addition to said viscogenic agent. When a viscogenic agent which is sparingly compatible or incompatible with the matrix components is employed for coating, the solid composition can be provided 25 with a film in which the viscogenic agent has been strategically dispersed. The coating material may further contain additives. In any of the above manufacturing processes, it is preferable to prevent infiltration of moisture.

30 The water-insoluble (hydrophobic) polymer includes but is not limited to ethylcellulose (FMC, Asahi Chemical), aminoalkyl methacrylate copolymer (Eudragit™ E100, Rhein-Pharma), aminoalkyl methacrylate copolymer (Eudragit™ RS, RL-100L, RS-300, RL-30D, RL-PO, RS-PO, 35 Röhm-Pharm). Those hydrophobic polymers can be used independently or as a mixture of two or more different

species.

The proportion of the viscogenic agent in the coating material may for example be about 0.005 to about 100 weight %, preferably about 0.05 to about 95 weight %, more preferably 5 about 0.05 to about 30 weight %, and still more preferably about 1 to about 10 weight %, based on the whole solid fraction of the coating material.

When at least one of said polyglycerol fatty acid ester, lipid, and hydrophobic polymer is used in 10 combination with said viscogenic agent for said coating, the proportion of the viscogenic agent based on the total weight of the solid matter of the coating material is about 0.005 to about 95 weight %, preferably about 0.5 to about 30 weight %, and more preferably about 5 to about 25 weight %.

15 Referring further to the coating material, two or more members selected from the class consisting of the polyglycerol fatty acid ester, lipid, and hydrophobic polymer can be used in combination. In this case, based on each part by weight of the whole polyglycerol fatty acid ester and/or lipid, the remaining component is used in a 20 proportion of about 0.0001 to about 1,000 parts, preferably about 0.01 to about 100 parts, and more preferably about 0.01 to about 10 parts.

The coating amount can be selected according to the 25 desired type of solid preparation and the desired strength of adhesion to the mucosa. For example, the coating amount for a solid preparation may be about 0.1 to about 30 weight %, preferably about 0.5 to about 20 weight %, more preferably about 0.5 to about 10 weight %, for tablets; about 0.1 to 30 about 50 weight %, preferably about 1 to about 20 weight %, for pills and granules; and about 0.1 to about 100 weight %, preferably about 1 to about 50 weight %, for fine granules.

Where necessary, the coating material may be 35 supplemented with common additives such as those mentioned hereinbefore. The coating material and the additive may be applied together or serially. The proportion of the

additive relative to the solid matter of the coating material is about 0.1 to about 70 weight %, preferably about 1 to about 50 weight %, and more preferably about 20 to about 50 weight %.

5        The coating technology that can be used includes a variety of per se known methods, such as pan coating, fluidized-bed coating, roll coating, and so on. When the coating material is a solution or dispersion containing water or an organic solvent, the spray coating method can 10 also be employed. The proportion of said water or organic solvent may for example be about 25 to about 99 weight %. There is no particular limitation on the kind of said 15 organic solvent. Thus, for example, alcohols such as methanol, ethanol, isopropyl alcohol, etc.; ketones such as acetone etc.; and halogenated hydrocarbons such as chloroform, dichloromethane, trichloroethane, etc. can be employed.

When the polyglycerol fatty acid ester and/or lipid is used for coating, the objective coated composition can 20 be obtained by melting the polyglycerol fatty acid ester and/or lipid, optionally together with other additives, under heating, emulsifying the melt with water, spray-coating the surface of a solid composition with the resulting emulsion, and drying the coat. An alternative 25 procedure comprises adding the coating material to the substrate solid composition preheated by hot air in a coating pan or the like and melt-spreading the coating.

The solid composition is coated generally at a temperature of about 25 to about 60°C and preferably at 30 about 25 to about 40°C.

The coating time can be judiciously selected with reference to the coating method, the characteristics and amount of the coating material, and characteristics of the substrate solid preparation.

35        Insofar as a sufficient adhesion to the gastrointestinal mucosa can be assured, the

gastrointestinal mucosa-adherent solid composition may, if necessary, be further coated with a conventional gastric coating agent or a water-soluble coating agent.

The gastrointestinal mucosa-adherent solid preparation includes but is not limited to fine granules, granules, pills, tablets manufactured by compressing said fine granules or granules with a tablet machine, and capsules manufactured by filling said fine granules or granules into suitable capsule shells. Among those preparations, fine granules and granules are preferred. The particle size distribution of said fine granules may for example be: particles measuring 10 to about 500  $\mu\text{m}$  in diameter accounting for not less than 75 weight %, particles larger than 500  $\mu\text{m}$  accounting for not more than 5 weight %, and particles smaller than 10  $\mu\text{m}$  accounting for not more than 10 weight %. The preferred distribution is 105 to about 500  $\mu\text{m}$  in diameter accounting for not less than 75 weight %, particles larger than 500  $\mu\text{m}$  accounting for not more than 5 weight %, and particles smaller than 74  $\mu\text{m}$  accounting for not more than 10 weight %. The particle size distribution of said granules may for example be about 500 to about 1410  $\mu\text{m}$  accounting for not less than 90 weight % and smaller than 177  $\mu\text{m}$  accounting for not more than 5 weight %.

The amount of the urease inhibitor in the pharmaceutical composition of the invention can be selected according to the intended dosage form and may for example be about 0.01 to about 95 weight %, preferably about 1 to about 95 weight %, more preferably about 10 to about 90 weight %, and for still better results, about 10 to about 50 weight %.

The pharmaceutical composition of the invention can be provided in a non-oral preparation. The non-oral preparation includes suppositories and preparations for external application.

The suppositories may be rectal suppositories or

vaginal suppositories, and the preparations for external application may for example be ointments (inclusive of creams), preparations for vaginal administration, transnasal or transdermal DDSs, etc.

5       Suppositories can be provided in oil-based or water-based solid, semi-solid, or liquid forms according to the per se known technologies.

10      The composition of the present invention is useful for the treatment of Helicobacter pylori-harboring mammals (e.g. feline, canine, bovine, equine, goat, monkey, human being, etc.). Any of the above-mentioned preparations exhibits marked efficacy in the clearance of Helicobacter pylori in such animals. The indication includes but is not limited to gastritis and gastrointestinal ulcer, stomach 15     cancer, and a particularly remarkable response can be obtained in the treatment of gastrointestinal ulcer.

20      The pharmaceutical preparation of the present invention are only sparingly toxic and can be administered orally or otherwise to mammals including human beings. The dosage of the preparation varies with different dosage forms, methods of administration, or species of active ingredient. In accordance with the present invention, the dosage of the urease inhibitor can be reduced to about one-half through about one-tenth of the usual dosage 25     required. For use in adult patients with gastric ulcer or duodenal ulcer, the preparation containing a compound of formula (I) is preferably administered in a daily dose of about 0.05 to about 100 mg/kg, preferably about 0.2 to about 100 mg/kg, more preferably about 0.2 to about 20 mg/kg, furthermore preferably about 0.1 to about 10 mg/kg, and for 30     the still better result, about 0.5 to about 10 mg/kg in terms of the active ingredient.

35      The pharmaceutical preparation of the present invention may further contain other active ingredient, such as antiulcerative agents, antimicrobial agents having anti-HP activity, antacids, gastric acid antisecretory

agents, etc. for the symptomatic relief or cure of 5  
gastrointestinal ulcers. As an alternative, the  
preparation of the invention can be used in combination with  
other independent preparations containing such other  
active drugs.

The antacid mentioned above includes but is not  
limited to aluminum hydroxide gel, sodium bicarbonate,  
aminoacetic acid, aluminum silicate, magnesium  
aluminometasilicate, magnesium silicate, magnesium oxide,  
10 magnesium hydroxide, magnesium carbonate, and calcium  
carbonate.

The gastric acid antisecretory agent mentioned above  
includes but is not limited to gastric proton pump  
inhibitors, histamine, and H<sub>2</sub> blockers. The proton pump  
15 inhibitor is any drug substance which inhibits secretion  
of gastric acid through direct or indirect inhibition of  
H/K-ATPase which is functioning as a proton pump in the acid  
secretory cells (parietal cells) of the gastric mucosa. As  
such, the proton pump inhibitor includes lansoprazole,  
20 omeprazole, pantoprazole, pariprazole sodium,  
leminoprazole, TY-11345, TU-199, FPL-65372, BY-686, tannic  
acid, ellagic acid, ebselen, AHR-9294, cassigarol-A,  
bafilomycin, Y-25942, xanthoangelol E, SKF-96356,  
epigallocatechin gallate, WY-27198, T-330, and SK&F-20054.  
25 The H<sub>2</sub> blocker includes but is not limited to cimetidine,  
ranitidine, amotidine, loctidine, and their derivatives  
and salts. Those H<sub>2</sub> blockers can be produced by the  
processes described in USP 3,950,333, USP 4,283,408, USP  
4,128,658, etc. or any processes analogous thereto.

30 The antimicrobial agents having anti-HP activity and  
antiulcerative agents which can be used include the  
following and other substances.

The antimicrobials mentioned above include but are  
not limited to penicillins (e.g. amoxicillin,  
35 benzylpenicillin, piperacillin, mecillinam, etc.),  
cephalosporins, macrolides (e.g. erythromycin,

clarithromycin, roxithromycin, azithromycin, etc.), tetracyclines (e.g. tetracycline, minocycline, etc.), aminoglycosides (e.g. gentamicin, amikacin, streptomycin, etc.), bismuth salts (e.g. bismuth acetate, bismuth citrate, 5 bismuth salicylate, etc.), imidazoles (metronidazole, tinidazole, miconazole, etc.), quinolones (e.g. ofloxacin, cyproxane, etc.), and tryptophanyl-t-RNA synthase inhibitors (e.g. indolmycin etc.). Particularly preferred are penicillins, macrolides, imidazole compounds, 10 and tryptophanyl-t-RNA synthase inhibitors. In particular, amoxicillin, clarithromycin and indolmycin are preferred.

As said antiulcerative agents, mucosal protectant antiulcerative agents, for instance, can be used. The 15 mucosal protectant antiulcerative agent which can be used includes but is not limited to (z)-7-[(1R,2R,3R)-2-[(E)-(3R)-3-hydroxy-4,4-dimethyl-1-octenyl]-3-methyl-5-oxocyclopentyl]-5-heptenoic acid (trimoprostil, ulstar), 1-butyric acid-7-(L-2-aminobutyric acid)-26-L-aspartic 20 acid-27-L-valine-29-L-alaninecalcitonin (elcatonin), 3-ethyl-7-isopropyl-1-azulene sulfonate sodium (egualen sodium).

The pharmaceutical preparations of the present invention can also be used in conjunction with other 25 preparations containing the above active ingredients.

As described above, the pharmaceutical preparations of the present invention are effective in the prevention and treatment of various gastrointestinal diseases (e.g. gastritis, duodenal ulcer, stomach ulcer, chronic 30 gastritis, etc.) associated with microorganisms inducing toxic reactions in the gastrointestinal tract, particularly Helicobacter pylori, at low doses.

Furthermore, in accordance with the present invention, phosphoric amide derivatives which are unstable 35 to water and acid can be pharmaceutically stabilized.

MODE OF WORKING THE INVENTION

The following reference examples, working examples, and test examples illustrate the present invention in further detail, however these examples should by no means 5 be construed as limiting the scope of the invention.

Reference Example 15-Methyl-2-thiophenecarboxamide

To 50 ml of acetic acid were added 2.6 g (0.1 M) of 10 5-methyl-2-thiophenecarbaldehyde, 8.3 g (0.12 M) of hydroxylamine hydrochloride, and 9.8 g (0.12 M) of sodium acetate, and the mixture was refluxed for 13-15 hours. After the starting compound ceased to be detected by liquid 15 chromatography (HPLC) (retention time ca 13 min.), the reaction mixture was concentrated under reduced pressure to about half its initial volume. To this concentrate was added 100 ml of concentrated hydrochloric acid and the reaction was carried out at 60°C for 4 hours. After completion of the reaction, the reaction mixture was 20 diluted with 100 ml of water and stirred under ice cooling for 30 minutes. The resulting crystals were collected by filtration and rinsed with 100 ml of iced water to provide 11.6 g (82%) of 5-methyl-2-thiophenecarboxamide (HPLC retention time: ca 4 min.).

25 HPLC conditions

Column: GL Science's Inertsil ODS-3, 5 µm,

4.6 x 150 mm

Eluent: acetonitrile:0.05 M potassium dihydrogen phosphate/water = 30:70

30 Detection wavelength: 231 nm

Flow rate: 1.0 ml/min.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ: 2.54 (3H, d, CH<sup>3</sup>), 7.01 (1H, dd, thiophene-4-H), 7.78 (1H, dd, thiophene-3-H).

35 Reference Example 2N-(diaminophosphinyl)-5-methyl-2-

thiophenecarboxamide

In 50 ml of toluene was suspended 7.6 g (47 mM) of 5-methyl-2-thiophenecarboxamide and while this suspension was stirred vigorously at room temperature, 10.9 g (50 mM) of phosphorus pentachloride was added. The mixture was heated at 65°C and stirred for 30 minutes. Then, under ice cooling, 2.0 ml of formic acid was added dropwise. The mixture was stirred at 25°C for 30 minutes and then concentrated under reduced pressure to remove the toluene. The residue was dissolved in 100 ml of tetrahydrofuran (THF), and 17.1 ml of 25% aqueous ammonia was added under ice cooling. The mixture was stirred at 25°C for 30 minutes, after which 100 ml of toluene was added, and the resulting crystals were recovered by filtration. The crystals were rinsed with 50 ml of THF and 50 ml of water and dried in vacuo to provide 6.78 g (64%) of N-(diaminophosphinyl)-5-methyl-2-thiophenecarboxamide.

m.p. 285-297°C (decomp.)

20 Reference Example 35-methyl-3-furancarboxylic acid

The mixture of 299 g of ethyl laevulinate, 142 g of ethylene glycol, 338 g of ortho triethyl formate, and 1 g of paratoluene sulfonic acid mono hydrate was stirred for 72 hours. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with 500 ml of ethyl ether, followed by rince with 1N sodium hydroxide, saturated sodium carbonate, and then water. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give 374 g of the colorless oily compound. 168 g of potassium t-butoxide was added portionwise to a diethylether solution of 181 g of the above-described compound and 222 g of ethyl formate at room temparature, then after addition, stirred for 15 hours at room temparature. The reaction mixture was added to ice, then was acidified with conc-hydrochloric acid under ice

cooling. After separation, the aqueous layer was extracted with ethyl ether. The organic layer was combined, and was concentrated under reduced pressure. 400 ml of acetone and 40 ml of 0.5 N sulfuric acid was added to the residue, and was refluxed for 30 min. The reaction mixture was concentrated under reduced pressure, and the residue was added to water and extracted with ethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in 100 ml of ethyl ether. The solution was added to 200 g of anhydrous polyphosphate and stirred for 20 min at 50 °C. The reaction mixture was cooled to room temperature and then iced water was added, and then the mixture was stirred for 10 min, extracted with ethyl ether, washed with water, dried over anhydrous magnesium sulfate, and then removed solvent. To give 95 g of brown oily substance, to the substance was added 300 ml of water and 35 g of sodium hydroxide and then stirred for 2 hours at room temperature. The reaction mixture was cooled and acidified with conc-hydrochloric acid and then stirred for 2 hours under ice cooling. To provide 44 g of 5-methyl-3-furancarboxylic acid as a colorless crystals, the precipitated solid was filtered.

25 Reference Example 45-methyl-3-furancarboxamide

5-methyl-3-furancarboxylic acid (0.95 g) was dissolved in tetrahydrofuran (30 ml), and N,N-dimethylformamide (3 drops) was added. Oxalyl chloride (1.0 g) was added dropwise at room temperature, and the mixture was stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in ethyl acetate (20 ml). The resulting solution was added dropwise to a mixture of 25% aqueous ammonia (30 ml) and ethyl acetate (100 ml) with stirring under ice-cooling. The resulting mixture was stirred at

room temperature for 3 hours, and then the mixture was washed with water and dried over anhydrous magnesium sulfate to remove the solvent. The residue was crystallized from aceton-isopropylether to provide 240 mg of 5-methyl-3-furancarboxamide.

5 mp 123-124 °C.

$^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 2.22 (3H, d,  $J=1.2$  Hz), 5.80 (2H, br, s), 7.23 (1H,  $J=1.2$  Hz), 7.85 (1H, D,  $J=1.2$  Hz)

10 Reference Example 5

N-(diaminophosphinyl)-5-methyl-3-furancarboxamide

5-Methyl-3-furancarboxamide (0.94 g) was suspended in toluene (10 ml), and phosphorus pentachloride (1.6 g) was added portionwise. The mixture was heated to 70 °C, 15 stirred for 30 minutes and then cooled to room temperature. Formic acid (0.35 g) was added dropwise, and the mixture was stirred at room temperature for 20 minutes. Then, hexane (30 ml) was added, and the mixture was stirred for 15 minutes. Precipitated crystals were collected by 20 filtration, washed with hexane, and dried to give 1.1 g of crystals. The crystals were dissolved in tetrahydrofuran (50 ml) and ammonia gas was introduced under ice-cooling for 30 minutes. The mixture was stirred at room temperature for 50 minutes. Ethyl ether (50 ml) was added and stirred 25 for 20 minutes. Precipitate was collected by filtration, washed with water, and dried. The obtained solid was recrystallized from methanol-ethyl ether to give N-(diaminophosphinyl)-5-methyl-3-furancarboxamide (0.39 g) as colorless crystals.

30 mp 168-170 °C.

Elemental analysis for  $\text{C}_6\text{H}_{10}\text{N}_3\text{O}_3\text{P}$

Calcd : C, 35.48; H, 4.96; N, 20.69.

Found : C, 35.42; H, 4.90; N, 20.42.

$^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ )  $\delta$  : 2.12 (3H, s), 4.12 (4H, br s), 7.48 (1H, s), 35 8.44 (1H, s), 9.07 (1H, d,  $J=7.6$  Hz).

Reference Example 62-methyl-3-furancarboxylic acid

2-Methyl-3-furancarboxylic acid ethyl ester (10 g) was dissolved in ethanol (70 ml), and 1N aqueous sodium hydroxide (78 ml) was added. The mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure. The residue was dissolved in water and washed with diethyl ether. The aqueous layer was acidified with 1N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water and saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Precipitated crystals were collected by filtration with diisopropyl ether to give 2-methyl-3-furancarboxylic acid (5.5 g) as crystals.

mp 101-102 °C.

Reference Example 72-methyl-3-furancarboxamide

20 2-methyl-3-furancarboxamide was synthesized in the similar manner as Reference Example 4.

mp 87-88 °C.

Reference Example 8N-(diaminophosphinyl)-2-methyl-3-furancarboxamide

25 2-Methyl-3-furancarboxamide (2.0 g) was suspended in toluene (30 ml), and phosphorus pentachloride (3.5 g) was added portionwise. The mixture was heated to 70 °C, stirred for 30 minutes, and then cooled to room temperature. Formic acid (0.74 g) was added dropwise, and the mixture was stirred at room temperature for 30 minutes. Hexane (20 ml) was added, and the resulting mixture was stirred for 10 minutes. Precipitated crystals were collected by filtration, washed with hexane and dried to give 3.3 g of crystals. The crystals were dissolved in tetrahydrofuran (100 ml), and ammonia gas was introduced under ice-cooling

for 30 minutes. The mixture was stirred at room temperature for 1 hour, and diethyl ether (100 ml) was added. The resulting mixture was stirred for 10 minutes, and precipitate was collected by filtration, washed with water and dried. The obtained solid was recrystallized from methanol to give N-(diaminophosphinyl)-2-methyl-3-furancarboxamide (0.85 g) as colorless crystals.  
5 mp 249-253 °C (decomp.).

Elemental Analysis for C<sub>6</sub>H<sub>10</sub>N<sub>3</sub>O<sub>3</sub>P  
10 Calcd : C, 35.48; H, 4.96; N, 20.69.

Found : C, 35.41; H, 4.86; N, 20.68.

<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 2.52(3H,s), 4.13(4H,s),  
7.17(1H,d,J=2.0Hz), 7.50(1H,d,J=2.0Hz),  
9.00(1H,d,J=7.4Hz).

15  
Reference Example 9  
3,5-dimethyl-2-furancarboxamide  
3,5-dimethyl-2-furancarboxamide was synthesized in the similar manner as Reference Example 4.  
20 mp 141-142 °C

Reference Example 10  
N-(diaminophosphinyl)-3,5-dimethyl-2-furancarboxamide  
25 N-(diaminophosphinyl)-3,5-dimethyl-2-furancarboxamide was synthesized in the similar manner as Reference Example 5.  
mp 189-191 °C

Elemental Analysis for C<sub>7</sub>H<sub>12</sub>N<sub>3</sub>O<sub>3</sub>P  
30 Calcd : C, 38.72; H, 5.57; N, 19.35.  
Found : C, 38.36; H, 5.31; N, 19.24.  
<sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 2.24(2H,s), 2.28(3H,s), 4.15(4H, br s), 6.17(1H,s), 8.09(1H,d,J=7.8Hz)

35 Reference Example 11  
3,5-dimethyl-2-thiophenecarboxamide

3,5-dimethyl-2-thiophenecarboxamide was synthesized in the similar manner as Reference Example 4.  
mp 141-142 °C

5           Reference Example 12

N-(diaminophosphinyl)-3,5-dimethyl-2-thiophenecarboxamide

N-(diaminophosphinyl)-3,5-dimethyl-2-thiophenecarboxamide was synthesized in the similar manner  
10          as Reference Example 5.

mp 160-162 °C

Elemental Analysis for C<sub>7</sub>H<sub>12</sub>N<sub>3</sub>O<sub>2</sub>

Calcd : C, 36.05; H, 5.91; N, 18.02.

Found : C, 35.86; H, 5.16; N, 17.97.

15          <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) δ : 2.37(3H,s), 2.41(3H,s), 4.13(4H, br s), 6.68(1H,s), 8.31(1H,br s)

Example 1

20          Production of a urease inhibitor-containing  
gastrointestinal mucosa-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>,  
Sakamoto Yakuhan Kogyo Co., Ltd.) (86.0 g) was melted at 84°C.  
To this melt, 4.0 g of N-(diaminophosphinyl)-5-methyl-  
2-thiophenecarboxamide (hereinafter referred to as  
25          compound-A) and 10.0g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104,  
Wako Pure Chemical Industries Ltd.) were serially added and  
the mixture was stirred for dispersion at a constant  
temperature of 84°C for 15 minutes. This molten mixture  
was dropped onto a 15 cm (di.) aluminum disk rotating at  
30          1950 rpm at a flow rate of 10 g/min, whereby spherical fine  
granules passing through a 42-mesh sieve but failing to pass  
through a 60-mesh sieve (hereinafter referred to briefly  
as 42/60-mesh) were obtained.

35          Example 2

Production of a urease inhibitor-containing gastric

mucosa-adherent preparation.

5 A mixture of hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial Co. Ltd.) (63.0 g) and behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.) (5.0 g) was melted at 84°C. To this melt, 4.0 g of compound-A, 8.0g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and 20.0 g of Curdlan (Takeda Chemical Industries, Ltd.) were serially added and the mixture was stirred for dispersion at a constant 10 temperature of 84°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 1950 rpm at a flow rate of 10 g/min, whereby 42/60-mesh spherical fine granules were obtained.

15 Example 3Production of a urease inhibitor-containing gastrointestinal mucosa-adherent preparation.

20 A mixture of hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial Co. Ltd.) (63.0 g) and behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.) (5.0 g) was melted at 84°C. To this melt, 4.0 g of compound-A) 8.0g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and 20.0 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred 25 for dispersion at a constant temperature of 84°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 1950 rpm at a flow rate of 10 g/min, whereby 42/60-mesh spherical fine granules were obtained.

30

Example 4Production of a urease inhibitor-containing gastrointestinal mucosa-adherent preparation.

35 Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.) (81.5 g) was melted at 84°C. To this melt, 0.5 g of compound-A, 8.0g of acrylic polymer

(HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and 10.0 g of Curdlan (Takeda Chemical Industries, Ltd.) were serially added and the mixture was stirred for dispersion at a constant temperature of 84°C for 15 minutes. This 5 molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 1950 rpm at a flow rate of 10 g/min, whereby 42/60-mesh spherical fine granules were obtained.

Example 5

10 Production of a urease inhibitor-containing gastric mucosa-adherent preparation.

A mixture of hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial Co. Ltd.) (54.0 g) and behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhan Kogyo Co., Ltd.) (1.0 g) was melted at 84°C. To this melt, 35.0 g of compound-A, 5.0g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and 5.0 g of Curdlan (Takeda Chemical Industries, Ltd.) were serially added and the mixture was stirred for dispersion at a constant 15 temperature of 84°C for 15 minutes. This molten mixture 20 was dropped onto a 15 cm (di.) aluminum disk rotating at 1950 rpm at a flow rate of 10 g/min, whereby 42/60-mesh spherical fine granules were obtained.

25 Example 6

Production of a urease inhibitor-containing gastrointestinal mucosa-adherent preparation.

A mixture of hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial Co. Ltd.) (35.0 g) and behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhan Kogyo Co., Ltd.) (1.0 g) was melted at 84°C. To this melt, 35.0 g of compound-A, 5.0g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and 5.0 g of low substituted 30 hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were 35 serially added and the mixture was stirred for dispersion at a constant temperature of 84°C for 15 minutes. This

molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 1950 rpm at a flow rate of 10 g/min, whereby 42/60-mesh spherical fine granules were obtained.

5                   Example 7

Production of a urease inhibitor-containing  
gastrointestinal mucosa-adherent preparation.

A mixture of hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial Co. Ltd.) (54.0 g) and behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(1.0 g) was melted at 84°C. To this melt, 35.0 g of compound-A, 5.0g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and 5.0 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 84°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 1950 rpm at a flow rate of 10 g/min, whereby 42/60-mesh spherical fine granules were obtained.

20

Example 8

Production of a urease inhibitor-containing gastric  
mucosa-adherent preparation.

Hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial Co. Ltd.) (76.0 g) was melted at 84°C. To this melt, 4.0 g of compound-A, 10.0g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and 10.0 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 84°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 1950 rpm at a flow rate of 10 g/min, whereby 42/60-mesh spherical fine granules were obtained.

35

Example 9

Production of a urease inhibitor-containing gastric mucosa-adherent preparation.

Hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial Co. Ltd.) (78.0 g) was melted at 84°C. To this melt, 4.0 g of compound-A, 8.0g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and 10.0 g Curdlan (Takeda Chemical Industries, Ltd.) were serially added and the mixture was stirred for dispersion at a constant temperature of 84°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 1950 rpm at a flow rate of 10 g/min, whereby 42/60-mesh spherical fine granules were obtained.

Test Example 1

The fine granules obtained in Example 9 were stored in a tight container at 40°C for 6 weeks and the stability of compound-A was investigated after 2, 4, and 6 weeks of storage.

Table 1

Storage period (weeks)	Content of compound-A (%)
0	100.0
2	99.1
4	103.4
6	100.0

20

It can be seen from Table 1 that compound-A remained stable in the preparation for 6 weeks.

Example 10

Production of a urease inhibitor-containing gastrointestinal mucosa-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(8.4 g) was melted at 80°C. To this melt, 0.1 g of N-(diaminophosphinyl)-2-methyl-3-furancarboxamide (hereinafter referred to as compound-B), 1.5g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical

Industries, Ltd.) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3,600 rpm at a flow rate 5 of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Example 11

10 Production of a urease inhibitor-containing gastrointestinal mucosa-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(8.4 g) was melted at 80°C. To this melt, 0.1 g of compound-B, 1.5g of acrylic polymer ammonium salt (HIVISWAKO<sup>TM</sup> 204, Wako Pure Chemical 15 Industries, Ltd.) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3,600 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules 20 were obtained.

Example 12

25 Production of a urease inhibitor-containing gastrointestinal mucosa-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(8.4 g) was melted at 80°C. To this melt, 0.1 g of compound-B, 1.5g of acrylic polymer sodium salt (EX214<sup>TM</sup>, The B.F. Goodrich Company) were 30 serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3,600 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

35 Example 13

Production of a urease inhibitor-containing

gastrointestinal mucosa-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(7.9 g) was melted at 80°C. To this melt, 0.1 g of compound-B, 1.0g of acrylic polymer ammonium salt (HIVISWAKO 204, Wako Pure Chemical Industries, Ltd.) and 1.0 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3600 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Example 14Production of a urease inhibitor-containing gastrointestinal mucosa-adherent preparation.

A mixture of behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(8.0 g) and hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial Co. Ltd.) (0.1 g) was melted at 85°C. To this melt, 0.1 g of compound-B, 0.8 g of acrylic polymer ammonium salt (HIVISWAKO<sup>TM</sup> 204, Wako Pure Chemical Industries, Ltd.) and 1.0 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3,600 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

30

Example 15Production of a urease inhibitor-containing gastrointestinal mucosa-adherent preparation.

A mixture of behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(8.0 g) and hydrogenated castor oil (Lubri wax<sup>TM</sup> 101, Freund Industrial

Co. Ltd.) (0.1 g) was melted at 85°C. To this melt, 0.1 g of N-(diaminophosphinyl)-5-methyl-3-furancarboxamide (hereinafter referred to as compound-C), 0.8 g of acrylic polymer ammonium salt (HIVISWAKO™ 204, Wako Pure Chemical Industries, Ltd.) and 1.0 g of low substituted hydroxypropylcellulose (LH-31™, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 85°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3,600 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Example 16

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

A mixture of behenic acid hexa (tetra) glyceride (HB-310™, Sakamoto Yakuhan Kogyo Co., Ltd.)(8.0 g) and hydrogenated castor oil (Lubri wax™ 101, Freund Industrial Co. Ltd.) (0.1 g) was melted at 85°C. To this melt, 0.1 g of compound-B, 0.8 g of acrylic polymer sodium salt (EX214™, The B.F. Goodrich Company) and 1.0 g of low substituted hydroxypropylcellulose (LH-31™, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 85°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3,600 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Example 17

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

A mixture of behenic acid hexa (tetra) glyceride (HB-310™, Sakamoto Yakuhan Kogyo Co., Ltd.)(8.0 g) and hydrogenated castor oil (Lubri wax™ 101, Freund Industrial Co. Ltd.) (0.1 g) was melted at 85°C. To this melt, 0.1

g of compound-C, 0.8 g of acrylic polymer sodium salt (EX214<sup>TM</sup>, The B.F. Goodrich Company) and 1.0 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred 5 for dispersion at a constant temperature of 85°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3,600 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

10

Example 18

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, 15 Sakamoto Yakuhin Kogyo Co., Ltd.)(56.0 g) was melted at 80°C. To this melt, 39.0 g of compound-B, 5.0 g of acrylic polymer (HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This 20 molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3960 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Example 19

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, 25 Sakamoto Yakuhin Kogyo Co., Ltd.)(56.0 g) was melted at 80°C. To this melt, 39.0 g of compound-B, 5.0 g of acrylic polymer 30 ammonium salt (HIVISWAKO<sup>TM</sup> 204, Wako Pure Chemical Industries, Ltd.) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3960 rpm at a flow rate 35 of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Example 20Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

5        Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>,  
Sakamoto Yakuhin Kogyo Co., Ltd.)(56.0 g) was melted at 80°C.  
To this melt, 39.0 g of compound-B, 5.0 g of acrylic polymer  
sodium salt (EX214<sup>TM</sup>, The B.F. Goodrich Company) were  
serially added and the mixture was stirred for dispersion  
10      at a constant temperature of 80°C for 15 minutes. This  
molten mixture was dropped onto a 15 cm (di.) aluminum disk  
rotating at 3960 rpm at a flow rate of 50 g/min, whereby  
42/119-mesh spherical fine granules were obtained.

15        Example 21

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>,  
Sakamoto Yakuhin Kogyo Co., Ltd.)(50.5 g) was melted at 80°C.  
20      To this melt, 39.0 g of compound-B, 4.0 g of acrylic polymer  
(HIVISWAKO<sup>TM</sup> 104, Wako Pure Chemical Industries, Ltd.) and  
6.5 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>,  
Shin-Etsu Chemicals) were serially added and the mixture  
was stirred for dispersion at a constant temperature of 80°C  
25      for 15 minutes. This molten mixture was dropped onto a 15  
cm (di.) aluminum disk rotating at 3960 rpm at a flow rate  
of 50 g/min, whereby 42/119-mesh spherical fine granules  
were obtained.

30        Example 22

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>,  
Sakamoto Yakuhin Kogyo Co., Ltd.)(50.5 g) was melted at 80°C.  
35      To this melt, 39.0 g of compound-B, 4.0 g of acrylic polymer  
ammonium salt (HIVISWAKO<sup>TM</sup> 204, Wako Pure Chemical

Industries, Ltd.) and 6.5 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This 5 molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3960 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Example 23

10 Production of a urease inhibitor-containing gastrointestinal-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(50.5 g) was melted at 80°C. To this melt, 39.0 g of compound-B, 4.0 g of acrylic polymer 15 sodium salt (EX214<sup>TM</sup>, The B.F. Goodrich Company) and 6.5 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 20 cm (di.) aluminum disk rotating at 3960 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Example 24

25 Production of a urease inhibitor-containing gastrointestinal-adherent preparation.

Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>, Sakamoto Yakuhin Kogyo Co., Ltd.)(50.5 g) was melted at 80°C. To this melt, 39.0 g of compound-B, 2.0 g of acrylic polymer 30 sodium salt (EX214<sup>TM</sup>, The B.F. Goodrich Company) and 8.5 g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 35 cm (di.) aluminum disk rotating at 3960 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules

were obtained.

Example 25

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

5           Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>,  
Sakamoto Yakuhin Kogyo Co., Ltd.)(60.0 g) was melted at 80°C.  
To this melt, 30.0 g of compound-B, 6.0 g of acrylic polymer  
10          sodium salt (EX214<sup>TM</sup>, The B.F. Goodrich Company) and 4.0  
g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>,  
Shin-Etsu Chemicals) were serially added and the mixture  
was stirred for dispersion at a constant temperature of 80°C  
for 15 minutes. This molten mixture was dropped onto a 15  
15          cm (di.) aluminum disk rotating at 3960 rpm at a flow rate  
of 50 g/min, whereby 42/119-mesh spherical fine granules  
were obtained.

Example 26

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

20          Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>,  
Sakamoto Yakuhin Kogyo Co., Ltd.)(70.0 g) was melted at 80°C.  
To this melt, 20.0 g of compound-B, 6.0 g of acrylic polymer  
25          sodium salt (EX214<sup>TM</sup>, The B.F. Goodrich Company) and 4.0  
g of low substituted hydroxypropylcellulose (LH-31<sup>TM</sup>,  
Shin-Etsu Chemicals) were serially added and the mixture  
was stirred for dispersion at a constant temperature of 80°C  
for 15 minutes. This molten mixture was dropped onto a 15  
30          cm (di.) aluminum disk rotating at 3960 rpm at a flow rate  
of 50 g/min, whereby 42/119-mesh spherical fine granules  
were obtained.

Example 27

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

35          Behenic acid hexa (tetra) glyceride (HB-310<sup>TM</sup>,

Sakamoto Yakuhin Kogyo Co., Ltd.)(60.0 g) was melted at 80°C. To this melt, 30.0 g of compound-B, 2.0 g of acrylic polymer sodium salt (EX214™, The B.F. Goodrich Company) and 8.0 g of low substituted hydroxypropylcellulose (LH-31™, 5 Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 80°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) aluminum disk rotating at 3960 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules 10 were obtained.

Example 28

Production of a urease inhibitor-containing  
gastrointestinal-adherent preparation.

15 A mixture of behenic acid hexa (tetra) glyceride (HB-310™, Sakamoto Yakuhin Kogyo Co., Ltd.)(20.0 g) and hydrogenated castor oil (Lubri wax™ 101, Freund Industrial Co. Ltd.) (29.0 g) was melted at 85°C. To this melt, 39.0 g of compound-B, 4.0 g of acrylic polymer sodium salt 20 (EX214™, The B.F. Goodrich Company) and 8.0 g of low substituted hydroxypropylcellulose (LH-31™, Shin-Etsu Chemicals) were serially added and the mixture was stirred for dispersion at a constant temperature of 85°C for 15 minutes. This molten mixture was dropped onto a 15 cm (di.) 25 aluminum disk rotating at 3960 rpm at a flow rate of 50 g/min, whereby 42/119-mesh spherical fine granules were obtained.

Test Example 2

In vivo anti-*Helicobacter pylori* effect of the urease 30 inhibitor-containing gastrointestinal-adherent preparation.

Mongolian gerbils (MON/Jms/Gbs) infected with *Helicobacter pylori* (hereinafter sometimes referred to briefly as HP) were subcutaneously dosed with a 35 lansoprazole (hereinafter referred to briefly as LPZ)-containing 0.5% methylcellulose suspension. At 30 minutes

after administration, compound-B-containing gastrointestinal-adherent preparations obtained in Example 13, 14 (AdMMS-13, -14 in Table 2) or a 1.0% NaHCO<sub>3</sub>/0.5% methylcellulose suspension containing compound-B (Suspension in Table 2) was orally administered twice a day for 3 consecutive days at a dose of 0.3 mg/kg as compound-B for AdMMS or 3 mg/kg as compound B for the suspension. At 16 hours after the final dose, the stomach was excised and the gastric wall was homogenized and serial dilutions were plated on the HP selective medium. The inoculated medium was incubated for 4 days at 37°C under microaerobic conditions and the number of viable cells was counted. The results are shown in Table 2.

15 Table 2

Formulation	Dose (mg/kg)	Clearance rate
	Indolmycin	Cleared/total (%)
Control	0	0
Suspension	3	40
AdMMS-12	0.3	40
AdMMS-13	0.3	40

20 The compound-B-containing gastrointestinal-adhesive preparations showed an equivalent anti-HP effect at the dose of one tenth of the suspension.

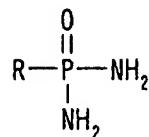
#### INDUSTRIAL APPLICABILITY

According to the present invention, phosphoric amide derivatives which are inherently unstable to moisture and acid can be stabilized in pharmaceutical composition. Those preparations are pharmaceutically meritorious in that an internal milieu with a relative humidity of not over 15% can be maintained over a long period of time under the usual storage conditions and, in addition, can be administered by the oral route.

Furthermore, the pharmaceutical composition or preparation provided with the property to adhere to the gastrointestinal mucosa in accordance with the present invention is capable of staying in the stomach to constantly release the active substance and, therefore, is very useful for the prevention and treatment of various gastrointestinal diseases associated with Helicobacter pylori, the microorganism known to do harm in the gastrointestinal, (such as gastritis, duodenal ulcer, stomach ulcer, and chronic gastritis).

CLAIMS

1. A pharmaceutical composition comprising a urease inhibitor and an oleaginous base.
- 5 2. A pharmaceutical composition according to Claim 1, which is a matrix.
3. A pharmaceutical composition according to Claim 1, which is a gastrointestinal mucosa-adherent composition.
- 10 4. A pharmaceutical composition according to Claim 1, which is a gastrointestinal mucosa-adherent matrix.
5. A pharmaceutical composition according to Claim 1, wherein the oleaginous base is a polyglycerol fatty acid ester and/or a lipid.
- 15 6. A pharmaceutical composition according to Claim 5, wherein the polyglycerol fatty acid ester is an ester of a polyglycerol having a degree of polymerization ranging from about 2 to about 20 with a fatty acid containing about 8 to about 40 carbon atoms.
- 20 7. A pharmaceutical composition according to Claim 5, wherein the HLB number of the polyglycerol fatty acid ester is about 1 to about 9.
- 25 8. A pharmaceutical composition according to Claim 5, wherein the amount of the polyglycerol fatty acid ester and/or the lipid used is about 20 to about 95 weight% to the total weight of the composition.
9. A pharmaceutical composition according to Claim 1, wherein the amount of the urease inhibitor used is about 10 to about 50 weight% to the total weight of the composition.
- 30 10. A pharmaceutical composition according to Claim 1, wherein the urease inhibitor is a phosphoric amide derivative or a salt thereof.
- 35 11. A pharmaceutical composition according to Claim 10, wherein the phosphoric amide derivative is a compound of the formula:

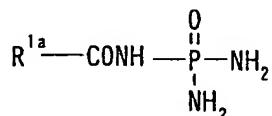


wherein R represents an amino group which may be substituted, or a salt thereof.

12. A pharmaceutical composition according to Claim 5 11, wherein R is a group represented by the formula:  
 $-\text{NHCOR}^1$

wherein R<sup>1</sup> represents hydrogen, a hydrocarbon group which may be substituted or a heterocyclic group which may be substituted.

10 13. A pharmaceutical composition according to Claim 10, wherein the phosphoric amide derivative is a compound of the formula:



15 wherein R<sup>1a</sup> represents a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, or a salt thereof.

14. A pharmaceutical composition according to Claim 13, wherein R<sup>1a</sup> represents an aromatic hydrocarbon group or an aromatic heterocyclic group, each of which may be substituted.

20 15. A pharmaceutical composition according to Claim 13, wherein R<sup>1a</sup> represents a 5-membered aromatic heterocyclic group which may be substituted.

25 16. A pharmaceutical composition according to Claim 13, wherein R<sup>1a</sup> represents a thienyl group or a furyl group, each of which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-3</sub> alkyl group which may be substituted by 1 to 3 halogens, a C<sub>1-3</sub> alkoxy group, halogen, nitro, cyano, a (C<sub>1-6</sub> alkyl)carbonyl and (C<sub>1-6</sub> alkyl)sulphonyl.

30 17. A pharmaceutical composition according to Claim 13, wherein R<sup>1a</sup> represents a thienyl group or a furyl group,

each of which is substituted by one or two C<sub>1-3</sub> alkyl groups.

18. A pharmaceutical composition according to Claim 1, wherein the urease inhibitor is N-(diaminophosphinyl)-5-methyl-2-thiophenecarboxamide or a 5 salt thereof.

19. A pharmaceutical composition according to Claim 1, wherein the urease inhibitor is N-(diaminophosphinyl)-2-methyl-3-furancarboxamide or a salt thereof.

10 20. A pharmaceutical composition according to Claim 1, wherein the urease inhibitor is N-(diaminophosphinyl)-5-methyl-3-furancarboxamide or a salt thereof.

15 21. A pharmaceutical composition according to Claim 1, wherein the urease inhibitor is N-(diaminophosphinyl)-3,5-dimethyl-2-furancarboxamide or a salt thereof.

20 22. A pharmaceutical composition according to Claim 1, wherein the urease inhibitor is N-(diaminophosphinyl)-3,5-dimethyl-2-thiophenecarboxamide or a salt thereof.

25 23. A pharmaceutical composition according to Claim 4, wherein the matrix comprises a viscoelastic agent capable of being viscous with water.

24. A pharmaceutical composition according to Claim 4, which is a matrix coated by a coating material containing a viscoelastic agent.

29 25. A pharmaceutical composition according to Claim 23, wherein the amount of the viscoelastic agent used is about 0.5 to about 30 weight% to the total weight of the composition.

30 26. A pharmaceutical composition according to Claim 23 or 24, wherein the viscoelastic agent is an acrylic polymer or a salt thereof.

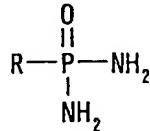
35 27. A pharmaceutical composition according to Claim 9, wherein the urease inhibitor is an anti-Helicobacter

pylori substance.

28. A pharmaceutical composition according to Claim 27, which is a preparation for a prophylaxis, a treatment, or a prevention of relapse of a Helicobacter pylori related gastrointestinal disease.

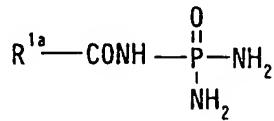
29. A pharmaceutical composition according to Claim 23, which comprises (i)an urease inhibitor, (ii)an polyglycerol fatty acid ester and/or a lipid, and (iii)an acrylic polymer or a salt thereof.

10 30. A pharmaceutical composition according to Claim 29, wherein (i)the urease inhibitor is a compound of the formula:



15 wherein R represents an amino group which may be substituted, or a salt thereof, (ii)the polyglycerol fatty acid ester and/or a lipid is behenic acid hexa(tetra)glyceride and/or tetraglycerol polyricinolate, and (iii)the molecular weight of the acrylic polymer is about  $20 \times 10^4$  to about  $600 \times 10^4$ .

20 31. A pharmaceutical composition according to Claim 29, wherein (i)the urease inhibitor is a compound of the formula:



25 wherein R<sup>1a</sup> represents a cyclic hydrocarbon group which may be substituted or a heterocyclic group which may be substituted, or a salt thereof, (ii)the polyglycerol fatty acid ester and/or a lipid is behenic acid hexa(tetra)glyceride and/or tetraglycerol polyricinolate, and (iii)the molecular weight of the acrylic polymer is about  $20 \times 10^4$  to about  $600 \times 10^4$ .

30 32. A pharmaceutical composition according to Claim 30, wherein R<sup>1a</sup> represents a thienyl group or a furyl group,

each of which may be substituted by 1 to 3 substituents selected from the group consisting of a C<sub>1-3</sub> alkyl group which may be substituted by 1 to 3 halogens, a C<sub>1-3</sub> alkoxy group, halogen, nitro, cyano, a (C<sub>1-6</sub> alkyl)carbonyl and (C<sub>1-6</sub> alkyl)sulphonyl.

5 33. A pharmaceutical composition according to Claim 30, wherein R<sup>1a</sup> represents a thiienyl group or a furyl group, each of which is substituted by one or two C<sub>1-3</sub> alkyl group.

10 34. A pharmaceutical composition according to Claim 1, which is used in combination with an antibiotic and/or an antacid and/or an acid secretion inhibitor .

35. An anti-Helicobacter pylori composition which comprises the pharmaceutical composition according Claim 1.

15 36. A pharmaceutical composition for a prophylaxis, a treatment, and a prevention of relapse of a Helicobacter pylori related gastrointestinal disease, comprising the pharmaceutical composition according Claim 1.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 98/01283

A. CLASSIFICATION OF SUBJECT MATTER  
 IPC 6 A61K31/00 A61K9/16 A61K47/14 A61K47/34

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category <sup>2</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	EP 0 443 572 A (TAKEDA CHEMICAL INDUSTRIES LTD) 28 August 1991 see the whole document ---	1-20, 22-36
Y	EP 0 642 797 A (TAKEDA CHEMICAL INDUSTRIES LTD) 15 March 1995 see the whole document ---	1-20, 22-36
Y	EP 0 514 008 A (TAKEDA CHEMICAL INDUSTRIES LTD) 19 November 1992 see the whole document ---	1-20, 22-36
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

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Date of the actual completion of the international search

6 July 1998

Date of mailing of the international search report

16/07/1998

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## INTERNATIONAL SEARCH REPORT

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PCT/JP 98/01283	

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	---	3-8, 23-26
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